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## Original Communications

# PROMIN IN THE TREATMENT OF SOME ACUTE INFECTIONS

JOHN A. TOOMEY, M.D., AND FREDERICK E. ROACH, M.D.
CLEVELAND, OHIO

PROMIN* is one of several new chemotherapeutic drugs now being investigated in various clinics.[1] It was first used in this hospital, the Division of Contagious Diseases, about a year ago. At first it was given orally, but because of erratic absorption, frequent anorexia, mild delirium, and the dusky, slatish type of cyanosis which occurred in one-sixth of the patients, its use was discontinued. Later, it was tried subcutaneously, but because the injections caused "burning" and local discomfort, this method of administration was stopped also. We then administered the drug intravenously and the toxic effects were so insignificant that we were encouraged to proceed further. This paper is a record of the results following the use of promin.

In order that the figures would be comparable, it was decided to give all of our patients, irrespective of age or sex, 5 Gm. of the drug intravenously three times a day for three days. A hemoglobin estimation and red blood cell and differential cell counts were taken before the administration of promin and after the ninth dose. The urea nitrogen content of the blood was determined. A blood promin level was estimated in most instances after the second to the fourth dose and after the sixth to the tenth dose.

In all, 154 patients were treated. They had streptococcic infections such as erysipelas, the complications of scarlet fever, and infections of the upper respiratory tract such as nasopharyngitis, sinusitis, tonsillitis, etc. There were two groups. Group I (95 cases) included fifty-four patients with follicular tonsillitis, herpes zoster, streptococcus pharyngitis, sinusitis, other infections of the respiratory tract including those of the ear, and cervical adenitis not secondary to scarlet fever; twenty-seven with scarlet fever with complications such as adenitis, mastoiditis, etc.; ten with bronchial or lobar pneumonia; two with diffuse cellulitis; one with anemia, probably secondary to some upper respiratory infec-

From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

*Supplied by Parke, Davis & Co.

tion; and one with erythema multiforme. Thirty-four of these had excellent responses, i.e., the temperature abruptly came down to normal within from twelve to twenty-four hours, and the subjective symptoms were improved concurrently; twenty-four had good responses, i.e., the temperature came down by lysis within forty-eight hours and the subjective symptoms were improved within twenty-four hours; eighteen had fair responses; sixteen had no benefit whatever; and three were not very sick on admission. Most of those that were not benefited by the drug had a complication of scarlet fever, and six of them had been given the drug subcutaneously or orally. Excluding the patients not ill on admission, seventy-six, or 82 per cent, of ninety-two had measurable clinical benefits from the drug.

In Group II were fifty-nine patients with erysipelas, twenty-nine of whom had excellent, fourteen good, and two fair, results. Five had no benefit; two died, one of whom had a secondary cavernous sinus thrombosis and one a carcinoma; and seven were not very sick on admission. Excluding the seven patients not ill on admission, forty-five, or eighty-six per cent, of the fifty-two remaining were benefited by the drug.

Momentary nausea was experienced by approximately 20 per cent of the patients while the needle was still in place and the drug was being injected; if the administration of the drug was prolonged over a period of approximately ten minutes, this percentage became distinctly smaller. Only occasionally did a patient vomit at the time of injection, and, in most instances, it was felt that this happened because the drug was injected too rapidly. This immediate nausea and vomiting are not to be confused with those reactions which occurred later.

The following complications occurred: rash, four cases; cyanosis, ten; nausea, nine; vomiting, four; nausea and vomiting, two; headache, two; vertigo, one. Six patients showed some decrease in hemoglobin, but it is questionable as to whether the drug was responsible for this condition. Twenty-four had been treated subcutaneously or orally, and this accounted for a great number of the complications just mentioned: rash, one case; cyanosis, seven; nausea, three; vomiting, three; vertigo, one; and mental confusion, four. It can be seen thus that the reactions occurring after intravenous injection of the standard dose were minimal.

The rashes which appeared were maculopapulated scarlatiniform lesions, sparse in number, but generally distributed. There was slight cyanosis in practically every patient, but it was not remarkable save in ten patients whose color became a slatish-blue.

With a streptococcic infection, the hemoglobin naturally decreases. A drop of under 15 per cent might be considered due to the disease or infection itself. In six cases, the hemoglobin estimation went down to between 15 and 20 per cent. One of these patients had lacerations, a diffuse cellulitis, and abscesses of the leg caused by a streptococcus infection, and the decrease in hemoglobin might have been due to this; at least, the drug did not aggravate the condition. Another pa-

tient had erythema multiforme and had been sick for a long time; one with influenzal meningitis had received sulfanilamide and sulfapyridine previously; one had scarlet fever, mastoiditis, and adenitis; one, erysipelas with pretibial abscesses and pharyngitis; and one, lumbar, dorsal, and cervical abscesses and transverse myelitis due to *Streptococcus viridans*. Otherwise, there was no significant change in the hemoglobin counts. The total number of red cells and white cells was not changed materially. Curiously, in most instances there was an actual increase in the total number of red blood cells and the hemoglobin. One patient was admitted to the hospital with an infection of long duration and an anemia (decrease in total number of red blood cells and content of hemoglobin), either secondary to the infection or due to some other undetermined cause. The differential and the white blood counts, however, were normal. After administration of 45 Gm. of promin, the number of white blood cells dropped to 750. The drug was discontinued, and the patient responded promptly to the usual therapy.

Five patients had glomerulonephritis. They were treated as follows:

1. A 9-year-old male with scarlet fever developed glomerulonephritis on the twenty-eighth hospital day (twenty days after a total of 210 grains of sulfanilamide had been given). His temperature rose to 40° C. Despite the nephritis, promin was started and the temperature dropped.

2. On admission to the hospital, a 22-year-old male showed red blood cells, occasional casts, and a 3+ benzidine in the urine. He was given promin immediately despite the presence of red blood cells, after which the temperature promptly came down and the red blood cells disappeared.

3. On admission a 49-year-old male with erysipelas of the leg gave a positive benzidine reaction, with approximately 5 to 8 red blood cells per high power field and occasional casts in the urine. Temperature was 39.5° C. He was given promin; the temperature came down to 37.4° C. within thirty-six hours, and the urine became clear.

4. A 35-year-old female on admission showed a 4+ benzidine reaction in the urine, with red cells on microscopic examination, and a temperature of 39.4° C. She was given promin, following which the temperature came down to 37.5° C. within twenty-four hours and the urine became clear.

5. This was the case of the patient with influenzal meningitis who developed red blood cells in the urine after having had massive amounts of all sorts of chemotherapy and before the course of promin was started.

Ten of the patients treated died, a little over 6.4 per cent. These deaths were expected despite the use of drugs.

1. One patient (No. 218110), a 6-year-old female ill with influenzal meningitis, had been given large amounts of sulfapyridine (166.5 Gm.) and monohydrate sodium sulfapyridine (5.2 Gm.), and finally, as a last resort, 96 Gm. of promin intravenously.

2. An imbecile female (No. 217324), aged 14 years, at autopsy showed stomatitis, suppurative otitis media, acute purulent leptomeningitis due to *Streptococcus viridans*, bronchopneumonia, sinus thrombosis of the straight, cavernous, transverse, superior, inferior petrosal and of the left internal jugular vein, chronic petrositis, and sphenoid sinusitis. This patient received sulfanilamide, 26+ Gm., sulfapyridine, 14 Gm., and finally, promin, 6 Gm.

3. A 32-year-old male (No. 217568) had pneumococcus meningitis, Type I. He was operated upon for mastoiditis (left) and at autopsy showed localized abscesses in the cerebrum and in the thoracic and lumbar cord. He was given 21 Gm. of promin.

4. An 11-month-old female (No. 215272) with influenzal meningitis, purulent otitis media, and bronchopneumonia, received 234 Gm. of sulfapyridine, 78 Gm. of sodium sulfapyridine, and finally, 62 Gm. of promin, before succumbing to the infection twenty-nine days after admission.

5. One patient (No. 216135), a female, aged 39 years, died twenty-four hours after admission. At autopsy there were found encephalomalacia due to embolism, thrombosis of the superior cerebral veins, edema of the brain, chronic cystitis, chronic cholecystitis, cholelithiasis, and subserous fibromyoma of the uterus.

6. A 45-year-old male (No. 217585) who had erysipelas of the face, cellulitis about the eye, sinus thrombosis, and convulsions, died seventeen hours after admission. He had been given sulfanilamide before he came to the hospital and 6 Gm. of promin after admission.

7. One patient (No. 218434), a 50-year-old female ill with spreading bronchopneumonia of undetermined etiology, acute nasopharyngitis, and acute cervical adenitis, died seven days after admission. She had been given 25.5 Gm. sulfapyridine and 45 Gm. of promin.

8. A 28-year-old male (No. 217974) died forty-four days after admission. He had a lumbodorsal epidural abscess caused by *Streptococcus viridans*, a brain abscess, and transverse myelitis at the level of the sixth thoracic segment. Treatment in this case consisted of thoracic, cervical, and lumbar laminectomies and multiple transfusions. He received promin at first, and later sulfapyridine and sulfanilamide, with no effect.

9. A 45-year-old male (No. 196759), who at autopsy showed cellulitis, lymphangitis of the left leg, bronchopneumonia, Laënnec's cirrhosis of the liver, acute streptococcic pharyngitis and bronchitis, and erysipelas, died about thirty-one hours after admission. He had been given 8 Gm. of sulfanilamide, with no effect, and as a last resort, 0.5 Gm. of promin just before death.

10. A 73-year-old female (No. 194075), with squamous-cell carcinoma of the lip, erysipelas of the face, chronic cervical adenitis, bronchopneumonia, and rheumatoid arthritis of the hands and feet, received 10.5 Gm. of promin before death. This patient had been in the hospital and in a critical condition for three and one-half months.

## COMMENT

Approximately 1,500 injections of promin have been made and over 150 patients have been treated with this drug. Grain for grain, we found it to be less toxic than sulfanilamide. Patients seemed to tolerate it better than either sulfanilamide or sulfapyridine. It does not cause destruction of either the hemoglobin content or the red blood cells in the dosage recommended and when injected intravenously. It has a definite beneficial effect upon streptococcic infections, especially those of the upper respiratory tract, and erysipelas. No attempt was made to estimate its efficacy in the pneumonias caused solely by the pneumococcus organisms. Even when used in the presence of red blood cells in the urine caused by some infection, it did not aggravate the condition. The disadvantage in its use is that it has to be injected intravenously; its advantage is that it does not seem to produce crystals or concretions in the urinary tract.[2]

It must be remembered that in our clinical experiments we were giving each and every patient the same dose of the drug. If the temperature reactions in Fig. 1 are studied, it can be seen that treatment

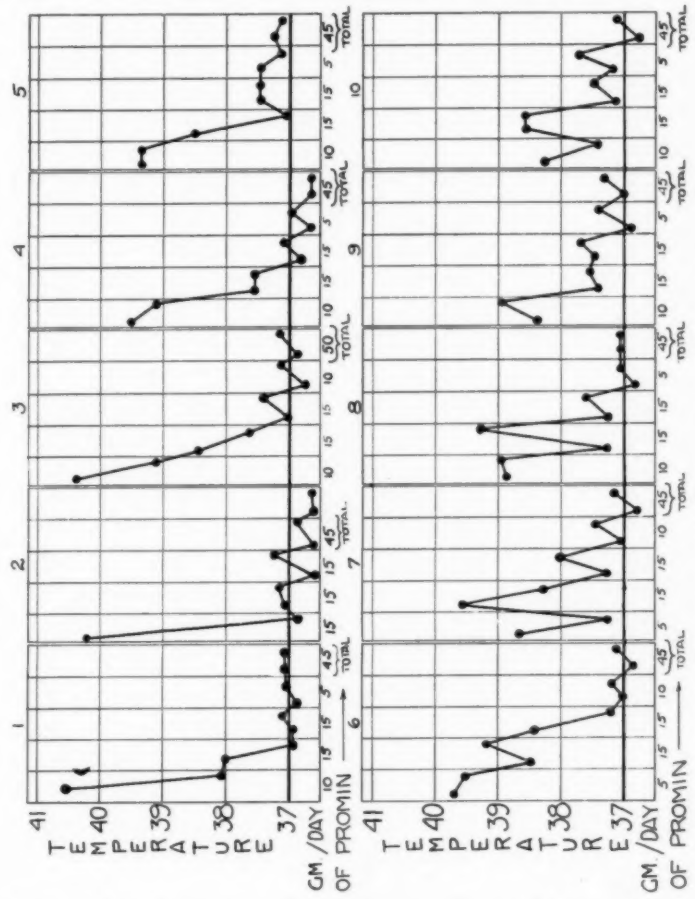


Fig. 1.—Temperature reactions after promin injections in ten patients.

might well have been stopped after lesser amounts of the drug had been given, in some instances after the third dose. Promin has been given simultaneously with sulfapyridine or sulfanilamide, with no apparent synergistic reactions.

## CONCLUSION

Promin, a new chemotherapeutic agent, is of value in the treatment of patients ill with conditions caused by streptococci.

## REFERENCES

1. Johnson, R. M.: Proc. Central Society for Clinical Research, Nov. 3 and 4, 1939.
2. Toomey, J. A., and Takacs, W. S.: J. Pediat. **18**: 10, 1941.

# BLOOD PROMIN LEVELS IN MAN

JOHN A. TOOMEY, M.D., AND MIRIAM E. DICE
CLEVELAND, OHIO

THE results following the administration of promin* in patients ill with streptococcic infections are described in a previous communication.[1] This paper is a report on the blood promin levels of eighty-five patients. There were great variations in the blood levels before it was decided to give the patients a standard dose of 5 Gm. of promin intravenously three times a day for three days. When this amount was given, the blood levels tended to become more uniform, although the results were not always identical.

## COMMENT

It was difficult to determine what should be the standard blood promin level. Nine of the eighty-five patients received less than 15 Gm. of the drug. The levels in these cases were below 4 mg. per 100 c.c. Ignoring these, fifty-eight of seventy-seven, or 72 per cent, had levels of 4 mg. per 100 c.c. or above at some time during the course of treatment.

Absorption was better in some patients than in others. Occasionally, even large amounts of the drug produced only low blood levels. One patient, No. 16, had a level of 100 mg. per 100 c.c. after 15 Gm. had been injected. Practically the same figures were obtained on rechecking. After 45 Gm. had been given, the level decreased to 68.8 mg. per 100 c.c. Patient 42, in whom the level was 20 mg. per 100 c.c., had influenzal meningitis and had been treated with sulfapyridine and sulfanilamide previous to administration of promin. The level of 30 mg. per 100 c.c. in patient 60 is not to be considered seriously, since the blood was taken too soon after the injection of promin. Twenty patients had a difference of at least 0.8 mg. per 100 c.c. between levels, the first level taken after the smaller dosage being higher than the second taken after a greater amount had been given. This might indicate early accumulation and temporary retention followed, in a few days, by rapid excretion.

Since, clinically, patients showed improvement after being given the standard dose mentioned above, perhaps a blood promin level between 4 and 10 mg. per 100 c.c. would be satisfactory from a clinical standpoint.

## REFERENCE

1. Toomey, John A., and Roach, Frederick E.: J. PEDIAT. **18**: 1, 1941.

From the Division of Contagious Diseases, City Hospital; the Department of Pediatrics, Western Reserve University; the Department of Pathology, City Hospital; and the School of Medicine, Western Reserve University.

*Supplied by Parke, Davis & Co.

TABLE I

| NO. | AGE | COLOR | SEX | TOTAL PROMIN GIVEN (GM.) | AMOUNT OF PROMIN WHICH HAD BEEN GIVEN AT TIME BLOOD LEVEL TAKEN (GM.) | BLOOD LEVEL TAKEN DAYS AFTER PROMIN STARTED | BLOOD PROMIN LEVELS (MG./100 C.C.) |
|---|---|---|---|---|---|---|---|
| 1 | 53 | W | F | 11 | 6 | 2 | 3.9 |
| | | | | | 11 | 3 | 3.7 |
| 2 | 57 | W | M | 8 | 8 | 2 | 2.7 |
| 3 | 29 | W | M | 16 | 8 | 2 | 1.4 |
| | | | | | 16 | 4 | 2.9 |
| 4 | 37 | W | M | 13 | 13 | 4 | 0.7 |
| 5 | 32 | W | M | 18 | 18 | 4 | 1.4 |
| 6 | 41 | W | F | 12 | 12 | 3 | 1.1 |
| 7 | 40 | W | M | 45 | 18 (1st course) | 3 | 2.1 |
| | | | | | 27 (2nd course) | 3 | 1.6 |
| 8 | 11 | W | F | 12 | 12 | 4 | 1.8 |
| 9 | 23 | W | F | 17 | 17 | 4 | 4.4 |
| 10 | 26 | W | M | 10 | 6 | 3 | 0.4 |
| 11 | 21 | W | F | 27 | 9 | 2 | 1.5 |
| | | | | | 27 | 4 | 1.4 |
| 12 | 14 mo. | W | M | 32 | 24 | 5 | 3.3 |
| 13 | 22 | W | M | 13 | 13 | 4 | 0.9 |
| 14 | 6 | W | M | 14 | 14 | 3 | 1.8 |
| 15 | 5 | W | M | 45 | 10 | 1 | 2.9 |
| | | | | | 45 | 3 | 8.8 |
| 16 | 29 | W | F | 45 | 15 | 1 | 100.0 |
| | | | | | 45 | 3 | 68.8 |
| | | | | | | 5 | 0.1 |
| | | | | | Fasting | 6 | trace |
| 17 | 23 | W | M | 40 | 10 | 2 | 4.4 |
| | | | | | 40 | 4 | 3.4 |
| 18 | 10 | W | F | 45 | 45 | 4 | 1.7 |
| 19 | 74 | W | F | 45 | 15 | 2 | 3.7 |
| | | | | | 45 | 4 | 8.4 |
| 20 | 44 | W | F | 45 | 15 | 2 | 3.0 |
| | | | | | 45 | 4 | 5.0 |
| 21 | 6 | W | M | 45 | 45 | 4 | 2.7 |
| 22 | 15 | W | F | 45 | 20 | 2 | 3.2 |
| | | | | | 45 | 4 | 1.6 |
| 23 | 35 | W | F | 45 | 15 | 2 | 3.3 |
| | | | | | 45 | 4 | 7.8 |
| 24 | 59 | W | F | 45 | 15 | 2 | 7.3 |
| | | | | | 45 | 4 | 7.0 |
| 25 | 42 | W | F | 45 | 15 | 2 | 4.4 |
| | | | | | 45 | 4 | 4.1 |
| 26 | 24 | W | F | 45 | 10 | 2 | 5.0 |
| | | | | | 45 | 4 | 4.1 |
| 27 | 49 | W | F | 36 | 18 (1st course) | 4 | 1.6 |
| | | | | | 18 (2nd course) | 4 | 0.8 |
| 28 | 12 | W | F | 45 | 15 | 2 | 4.2 |
| | | | | | 45 | 4 | 6.6 |
| 29 | 21 | W | F | 45 | 10 | 2 | 2.7 |
| | | | | | 45 | 11 | 0.7 |
| 30 | 55 | W | F | 75 | 9 (1st course) | 2 | 3.5 |
| | | | | | 18 | 4 | 4.1 |
| | | | | | 45 (2nd course) | 4 | 8.9 |

TABLE I—CONT'D

| NO. | AGE | COLOR | SEX | TOTAL PROMIN GIVEN (GM.) | AMOUNT OF PROMIN WHICH HAD BEEN GIVEN AT TIME BLOOD LEVEL TAKEN (GM.) | BLOOD LEVEL TAKEN DAYS AFTER PROMIN STARTED | BLOOD PROMIN LEVELS (MG./100 C.C.) |
|---|---|---|---|---|---|---|---|
| 31 | 43 | W | M | 45 | 20 | 2 | 8.7 |
| | | | | | 45 | 3 | 5.4 |
| 32 | 26 | W | M | 45 | 20 | 2 | 5.8 |
| | | | | | 45 | 4 | 2.0 |
| 33 | 44 | W | M | 45 | 15 | 2 | 4.4 |
| | | | | | 45 | 4 | 1.7 |
| 34 | 6 | W | M | 22 | 22 | 5 | 1.6 |
| 35 | 24 | W | F | 45 | 20 | 3 | 5.8 |
| | | | | | 45 | 4 | 4.6 |
| 36 | 40 | W | M | 45 | 20 | 2 | 3.2 |
| | | | | | 45 | 4 | 4.0 |
| 37 | 22 | W | M | 45 | 20 | 2 | 3.3 |
| | | | | | 45 | 4 | 4.5 |
| 38 | 50 | W | F | 45 | 20 | 2 | 7.2 |
| | | | | | 45 | 4 | 5.6 |
| 39 | 31 | W | F | 45 | 20 | 2 | 2.0 |
| | | | | | 45 | 4 | 5.0 |
| 40 | 3 | W | M | 45 | 20 | 2 | 5.8 |
| | | | | | 45 | 4 | 4.3 |
| 41 | 4½ | W | M | 45 | 25 | 3 | 8.0 |
| | | | | | 45 | 5 | 9.2 |
| 42 | 50 | W | F | 45 | 20 | 3 | 14.5 |
| | | | | | 45 | 5 | 20.0 (Died) |
| 43 | 19 | W | M | 24 | 24 | 4 | 0.9 |
| 44 | 78 | W | M | 45 | 20 | 2 | 6.4 |
| | | | | | 45 | 4 | 5.8 |
| 45 | 60 | W | F | 45 | 20 | 3 | 9.7 |
| | | | | | 45 | 5 | 10.4 |
| 46 | 63 | W | F | 45 | 25 | 3 | 10.2 |
| | | | | | 45 | 4 | 4.8 |
| 47 | 60 | W | M | 45 | 15 | 1 | 6.5 |
| | | | | | 45 | 4 | 4.9 |
| 48 | 28 | W | F | 45 | 15 | 2 | 5.2 |
| | | | | | 45 | 4 | 4.4 |
| 49 | 20 | W | F | 45 | 20 | 2 | 4.6 |
| | | | | | 45 | 4 | 6.0 |
| 50 | 19 | W | F | 45 | 20 | 2 | 5.7 |
| | | | | | 45 | 4 | 4.4 |
| 51 | 23 | W | F | 45 | 20 | 3 | 2.3 |
| | | | | | 45 | 4 | 2.2 |
| 52 | 21 | W | M | 45 | 20 | 2 | 1.7 |
| | | | | | 45 | 4 | 4.4 |
| 53 | 12 | W | M | 45 | 20 | 2 | 4.4 |
| | | | | | 45 | 4 | 5.2 |
| 54 | 28 | W | F | 45 | 20 | 2 | 9.0 |
| | | | | | 45 | 4 | 4.8 |
| 55 | 5½ | W | M | 35 | 20 | 2 | 9.4 |
| | | | | | 35 | 4 | 6.5 |
| 56 | 26 | W | M | 45 | 20 | 2 | 3.8 |
| | | | | | 45 | 4 | 1.7 |
| 57 | 40 | W | F | 45 | 20 | 3 | 2.6 |
| | | | | | 45 | 4 | 2.2 |
| 58 | 16 | B | F | 45 | 20 | 2 | 3.9 |
| | | | | | 45 | 4 | 3.6 |
| 59 | 63 | W | M | 40 | 20 | 2 | 2.1 |
| | | | | | 45 | 4 | 4.1 |

TABLE I—CONT'D

| NO. | AGE | COLOR | SEX | TOTAL PROMIN GIVEN (GM.) | AMOUNT OF PROMIN WHICH HAD BEEN GIVEN AT TIME BLOOD LEVEL TAKEN (GM.) | BLOOD LEVEL TAKEN DAYS AFTER PROMIN STARTED | BLOOD PROMIN LEVELS (MG./100 C.C.) |
|---|---|---|---|---|---|---|---|
| 60 | 39 | B | F | 90 | 15 (1st course) | 2 | 5.6 |
| | | | | | 45 | 4 | 4.1 |
| | | | | | 20 (2nd course) | 3 | 30.0 |
| | | | | | 45 | 4 | 5.4 |
| 61 | 25 | W | F | 45 | 20 | 2 | 3.7 |
| | | | | | 45 | 5 | 5.2 |
| 62 | 25 | W | F | 45 | 20 | 2 | 3.2 |
| | | | | | 45 | 4 | 7.1 |
| 63 | 17 | B | F | 45 | 20 | 3 | 4.2 |
| | | | | | 45 | 4 | 2.3 |
| 64 | 50 | W | M | 45 | 20 | 2 | 3.0 |
| | | | | | 45 | 4 | 6.3 |
| 65 | 47 | W | M | 45 | 20 | 2 | 3.0 |
| | | | | | 45 | 4 | 6.8 |
| 66 | 26 | W | F | 45 | 20 | 2 | 5.2 |
| | | | | | 45 | 4 | 6.2 |
| 67 | 40 | W | F | 45 | 20 | 2 | 17.2 |
| | | | | | 45 | 4 | 15.0 |
| 68 | 24 | W | M | 45 | 20 | 2 | 5.2 |
| | | | | | 45 | 4 | 3.4 |
| 69 | 55 | W | F | 75 | 20 | 2 | 2.2 |
| | | | | | 45 | 4 | 2.5 |
| | | | | | 65 | 5 | 3.8 |
| | | | | | 75 | 6 | 4.5 |
| 70 | 31 | W | F | 45 | 20 | 3 | 1.8 |
| | | | | | 45 | 4 | 2.2 |
| 71 | 13 | W | M | 45 | 20 | 2 | 3.7 |
| | | | | | 45 | 4 | 6.5 |
| 72 | 67 | W | F | 45 | 20 | 2 | 7.7 |
| | | | | | 45 | 4 | 5.4 |
| 73 | 40 | W | F | 45 | 15 | 2 | 6.6 |
| | | | | | 45 | 4 | 4.4 |
| 74 | 16 | B | M | 20 | 20 | 2 | 2.4 |
| 75 | 26 | W | F | 45 | 20 | 2 | 2.4 |
| | | | | | 45 | 4 | 4.0 |
| 76 | 52 | W | M | 45 | 20 | 2 | 4.2 |
| | | | | | 45 | 4 | 4.4 |
| 77 | 20 | W | F | 45 | 20 | 3 | 7.9 |
| | | | | | 45 | 4 | 5.7 |
| 78 | 6 | B | M | 45 | 20 | 2 | 7.1 |
| | | | | | 45 | 4 | 14.4 |
| 79 | 68 | W | M | 45 | 20 | 3 | 8.6 |
| | | | | | 45 | 4 | 9.0 |
| 80 | 43 | W | M | 45 | 20 | 3 | 7.4 |
| | | | | | 45 | 4 | 4.6 |
| 81 | 7 | W | F | 45 | 20 | 2 | 7.0 |
| | | | | | 45 | 4 | 9.2 |
| 82 | 7 | W | M | 45 | 20 | 2 | 5.5 |
| | | | | | 45 | 4 | 3.5 |
| 83 | 31 | W | F | 75 | 20 | 2 | 5.2 |
| | | | | | 45 | 4 | 6.2 |
| | | | | | 75 | 6 | 6.4 |
| 84 | 28 | W | M | 60 | 20 | 3 | 3.5 |
| | | | | | 45 | 4 | 8.0 |
| | | | | | 60 | 6 | 1.7 (Died) |
| 85 | 20 | W | F | 36 | 8 | 2 | 0.9 |
| | | | | | 36 | 3 | 0.2 |

# ATTEMPTS TO PRODUCE URINARY CONCRETIONS IN THE MONKEY WITH PROMIN

JOHN A. TOOMEY, M.D., AND WILLIAM S. TAKACS
CLEVELAND, OHIO

PROMIN,* a sodium salt of p, pi-diaminodiphenyl-sulfone-N, N′-di (dextrose sulfonate), with a structure as noted below,† is a new chemotherapeutic drug. It has been investigated clinically.[1, 2] The purpose of this work was to determine if this agent would produce urinary concretions in the *Macacus malatta* monkey. One of the authors (Toomey) has found that 45 Gm. of the drug given intravenously over a period of three days is well tolerated by the human being. This is about 0.9 Gm. per kilogram for persons weighing 50 kg.

*M. malatta* monkeys can be given such concentrations of promin without any reactions. Since the purpose of these experiments was to see if this drug would cause the formation of stones, massive amounts, i.e., 8 Gm. (5.33 Gm. or more per kilogram) were injected in twelve monkeys weighing from 1,200 to 1,500 Gm. Two animals weighing about 2,500 Gm. were given the same dose. Such an amount of the drug should cause a severe strain on the kidneys, for, if a patient weighing 50 kg. were to receive a comparative dose, approximately 266 Gm. (3,990 grains) of the drug would have to be given.

The fourteen animals were each given 0.5 Gm. of promin daily for four days, and then 1 Gm. daily for six days. All injections were made intramuscularly. Ten were sacrificed at the end of ten days and examined grossly and microscopically. Four were allowed to live a few days longer to note if any cumulative side effects would occur.

Three animals lost weight. There was an increase in the total number of white blood cells in ten of the fourteen animals; in seven, there was a decrease of at least 10 points in the hemoglobin content; in five, a small, but significant, decrease in the total number of red blood cells; in two, a slight increase in the blood urea nitrogen level, and in three, a definite increase above 20 mg. per cent, an obvious pathologic finding in the monkey. The blood promin level was variable, the highest being 38.4 mg. per 100 c.c.

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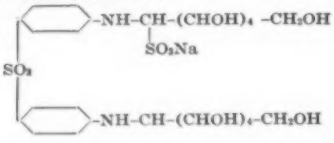
From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

*Supplied by Parke, Davis & Co.

†Structural formula:



It might appear that the relatively large amounts of this drug could cause hemopoietic changes. These experiments, however, do not prove this point, since the frequent bleedings for specimens might cause some decrease in the hemoglobin content and in the number of red blood cells.

Even with the massive doses used, five or more times as much as the largest dose recommended for human beings, there was no evidence of the formation of stones or crystals.* In experiments with sulfapyridine,[3] autopsy revealed crystals and concretions practically occluding the ureters, and it was assumed that the increase in the blood urea nitrogen levels was caused by blockage which prevented excretion. Here, however, there was an increase in blood urea nitrogen levels even in the absence of any such irritation. This fact raises the question as to whether or not the increase in the blood urea nitrogen levels may occur first, with the crystals being formed secondarily or, at least, concomitantly.

## CONCLUSION

Nearly six times the dose of promin recommended for human beings does not produce urinary concretions in *M. malatta* monkeys when injected intravenously.

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3. Toomey, J. A., Reichle, H. S., and Takacs, W. S.: J. PEDIAT. **16**: 179, 1940.

*Autopsies on most of these animals were done by the Department of Pathology, and the gross and microscopic findings will be reported by them elsewhere.

# DIET IN MALNUTRITION AND CELIAC DISEASE

## With Special Reference to the Use of Dextrose and Bananas

Genevieve Stearns, Ph.D., P. C. Jeans, M.D., Ruth Catherwood, and John B. McKinley
Iowa City, Iowa

THIS report concerns the results of a study of the energy need of undernourished children and of the most efficient distribution of calories among the foodstuffs for the correction of malnutrition.

From a study of adults, Strang, McClugage and Brownlee[1] concluded that malnutrition produces no digestive dysfunction and that gain in weight is dependent solely upon energy intake, which should be from 65 to 90 calories for each kilogram of actual weight. Their subjects did equally well with diets high in fat or high in carbohydrate. Utheim,[2] in a detailed study of malnutrition in infants, found a decreased digestive capacity for all of the energy components of the diet. Basal metabolic rates were little changed and the oxidative capacity of the infants was unimpaired. Low serum protein was the rule despite the accompanying dehydration. Similar findings have been reported by others. Dodd and Minot[3] noted the prevalence of low serum protein in chronically malnourished children; in some instances the condition was associated with edema which disappeared when the serum protein level increased. Fleming and Hutchinson[4] found that the proteins were best utilized and the carbohydrates least well utilized by athreptic infants. The malnutrition of celiac disease is known to be associated with impaired utilization of fats and complex carbohydrates, but with good utilization of protein.

This study deals only with the nutritional phases of malnutrition, and leaves out of consideration the psychic factors which often play a most important role in the ingestion of food. Some of our experimental subjects were chosen from relief rolls; for these, the difficulty was inability to obtain sufficient food. Fifteen children from 10 to 50 per cent underweight have been studied. Of these, eight were brought under care solely for experimental purposes; the remainder were children hospitalized for other conditions, but selected for study because of malnutrition. One of these latter children presented a behavior problem which included poor feeding habits. One child had chronic atrophic arthritis in an inactive stage; one child had a congenital malformation of the urinary tract, with a low-grade urinary infection. Three children had typical celiac disease; another child had a condition closely related

From the Department of Pediatrics, College of Medicine, State University of Iowa.
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to celiac disease, with intolerance for complex carbohydrates but not for fats, and had had diarrhea for two years. Many of the children, including all of those brought in exclusively for study, had some evidence of chronic upper respiratory infection consisting chiefly of hypertrophied or chronically diseased tonsils; no treatment for these conditions was undertaken until after the metabolic study was completed. A summary of the pertinent data concerning the subjects is shown in Table I.

Four types of diet were used, namely, "normal," "fat," "dextrose," and "banana." The "normal diet" was the customary average diet of our hospital. The "fat diet" contained 1.5 Gm. of fatty acid for each gram of potential glucose; this diet was small in bulk. The "dextrose diet" contained no starch and as little fat as was practicable; this diet was high in protein and contained the carbohydrate largely as dextrose. In the "banana diet," bananas were substituted for dextrose of the dextrose diet in terms of carbohydrate equivalence. All the diets were "complete" and were excellent or high in mineral and vitamin content.

The diets were weighed during the entire study, deductions being made for refused food, which also was weighed. Urine and feces were collected for five-day periods and analyzed, concurrently with the diets, for calcium, phosphorus, and nitrogen by methods previously reported.[5] The urines were analyzed also for creatinine, glucose, and acetone bodies.[6]

Each child was weighed daily on rising. Heights were measured frequently. In order to avoid errors due to posture, body length was measured in recumbency for children with lordosis and protruding abdomen.

## GAINS IN WEIGHT

The first group of experimental subjects consisted of five children, from 7 to 12 years of age, who were selected from relief rolls. Two of the children (S. H., H. H.) were given the fat diet, two (M. R., J. R.) the dextrose diet, and one (R. S.) the normal diet. The caloric intakes of the children were from 10 to 60 per cent above the levels usually recommended for their ages, the appetite being the limiting factor. The gains in weight are shown in Charts 1 and 2 and summarized in Table II. In Table II is indicated also the amount of energy intake designated as "normal" or "average" and used as a basis for comparison in this study.

One child only (M. R., 12 years), whose caloric intake was 50 per cent above average for her size and who was ingesting the dextrose diet, gained weight rapidly. For this child the original rate of gain was maintained during an attack of tonsillitis, but the weight became stationary after recovery. The gain for the fifteen-day period of this level of diet amounted to 1.6 kg., an average gain of more than 100 Gm.

TABLE I

SUBJECTS STUDIED

| NAME | SEX | AGE (YR.) | DISEASE* | TOTAL DAYS STUDIED | DAYS TEMPERATURE ELEVATED† | WEIGHT | | HEIGHT | | DIETS USED‡ | PER CENT UNDERWEIGHT§ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | FIRST (KG.) | FINAL (KG.) | FIRST (CM.) | FINAL (CM.) | | |
| A. W. | M | 1½ | Celiac | 81 | 15 | 8.1 | 11.6 | 79.4 | 82.5 | N B | 34 |
| R. Wt. | M | 3¼ | Malnutrition with diarrhea | 78 | 6 | 8.4 | 14.1 | 81 | 95.5 | D | 40 |
| A. A. | M | 4 | Celiac | 44 | 4 | 12.8 | 15.1 | 90 | 94.9 | D B | 14.5 |
| R. Ws. | M | 4 | | 8 | 0 | 14.6 | 15.2 | 106 | | B | 25 |
| J. W. | F | 5 | Chronic renal infection | 27 | 9 | 14.8 | 16.7 | 110 | | D | 13 |
| R. D. | M | 5 | | 29 | 11 | 14.9 | 16.0 | 105.3 | | B | 19 |
| E. M. | M | 6 | Celiac | 44 | 6 | 15.5 | 19.5 | 99.0 | 103 | D B | 12 |
| J. R. | M | 7 | | 53 | 7 | 19.0 | 22.3 | 119.0 | 119.7 | D N | 10 |
| R. S. | M | 8 | | 64 | 5 | 22.4 | 26.7 | 125.5 | 127 | N F | 11 |
| H. H. | M | 9 | | 65 | 0 | 20.9 | 30.0 | 130 | 131 | F D | 24 |
| D. M. | M | 9 | | 76 | 2 | 26.6 | 31.4 | 135.5 | 138 | D B | 14 |
| C. M. | M | 10 | | 42 | 5 | 27.9 | 29.4 | 143 | 145 | D B | 21 |
| M. B. | F | 11 | Atrophic arthritis, inactive | 58 | 4 | 28.5 | 34.3 | 147 | 147 | F B | 11 |
| M. R. | F | 12 | | 52 | 4 | 29.1 | 36.9 | 144 | 144.3 | D F | 18 |
| S. H. | M | 13 | | 64 | 1 | 28.4 | 36.2 | 143 | 145 | F D | 19 |

*Other than malnutrition.

†Rectal temperature above 100° F.

‡N, normal; F, fat; D, dextrose; B, banana. (See text for explanation.)

§Kornfeld standard for children under 6 years of age; Baldwin-Wood standard for children over 6 years of age.

TABLE II

GAINS IN WEIGHT IN RELATION TO CALORIC INTAKES

| NAME | AGE (YR.) | DIET | PER CENT UNDER-WEIGHT* | DAYS IN PERIOD | DAILY CALORIC INTAKE† | | AVERAGE WEIGHT GAIN (GM./DAY) | NORMAL WEIGHT GAIN (GM./DAY) |
|---|---|---|---|---|---|---|---|---|
| | | | | | CAL./KG. | PER CENT OF NORMAL | | |
| A.W. | 1½ | N | 34 | 10 | 210 | 210 | 20‡ | 6 |
| | | B | 31 | 68 | 180 | 180 | 47‡ | 6 |
| R.Wt. | 3¼ | D | 40 | 78 | 150 | 180 | 73‡ | 6 |
| A. A. | 4 | D | 14.5 | 22 | 135 | 160 | 36 | 6 |
| | | B | 10 | 23 | 170 | 200 | 61‡ | 6 |
| R.Ws. | 4 | B | 25 | 8 | 95 | 110 | 75 | 6 |
| E. M. | 6 | D | 12 | 22 | 155 | 210 | 109 | 6 |
| | | B | 9 | 23 | 140 | 190 | 65‡ | 6 |
| J. R. | 7 | $D_1$ | 10 | 20 | 85 | 110 | -20‡ | 7.5 |
| | | $D_2$ | 14 | 7 | 100 | 130 | 43 | |
| | | $D_3$ | 12 | 6 | 115 | 150 | 100 | |
| | | $N_1$ | 9 | 7 | 115 | 150 | 0 | |
| | | $N_2$ | 9 | 15 | 125 | 170 | 45 | |
| R. S. | 8 | $N_1$ | 11 | 15 | 90 | 130 | 13 | 7.5 |
| | | $N_2$ | 10.5 | 5 | 100 | 140 | 20 | |
| | | $N_3$ | 10 | 14 | 115 | 165 | 55‡ | |
| | | $F_1$ | 4 | 9 | 110 | 160 | -11 | |
| | | $F_2$ | 5 | 12 | 115 | 165 | 58 | |
| | | D | 1.5 | 6 | 110 | 160 | 330 | |
| H. H. | 9 | $F_1$ | 24 | 15 | 100 | 140 | 7 | 9 |
| | | $F_2$ | 24 | 6 | 115 | 165 | 17 | |
| | | $F_3$ | 23 | 8 | 125 | 180 | 137 | |
| | | D | 19 | 34 | 120 | 170 | 139 | |
| D. M. | 9 | D | 14 | 23 | 95 | 135 | 92 | 9 |
| | | B | 7 | 19 | 85 | 120 | 79 | |
| | | F | 2.5 | 17 | 90 | 130 | -12 | |
| | | B | 4.5 | 6 | 80 | 110 | 300 | |
| C. M. | 10 | D | 21 | 23 | 100 | 140 | 78‡ | 9 |
| | | B | 16 | 11 | 95 | 135 | 91 | |
| M. B. | 11 | F | 11 | 28 | 105 | 160 | 68 | 11 |
| | | B | 5 | 28 | 80 | 110 | 139 | |
| M. R. | 12 | $D_1$ | 18 | 17 | 100 | 150 | 95‡ | 9 |
| | | $D_2$ | 13 | 6 | 110 | 170 | 200 | |
| | | $F_1$ | 10 | 6 | 110 | 170 | -16 | |
| | | $F_2$ | 10 | 22 | 115 | 180 | 182 | |
| S. H. | 13 | $F_1$ | 19 | 8 | 105 | 160 | -25 | 10 |
| | | $F_2$ | 16.5 | 5 | 120 | 180 | 160 | |
| | | $F_3$ | 14 | 5 | 125 | 190 | 140 | |
| | | $F_4$ | 12.5 | 5 | 130 | 200 | 340 | |
| | | $D_1$ | 8.5 | 11 | 125 | 190 | 250 | |
| | | $D_2$ | 2 | 4 | 100 | 150 | -175 | |
| | | $D_3$ | 3.5 | 9 | 120 | 180 | 155 | |
| | | $D_4$ | 0 | 15 | 100 | 150 | 67 | |

*At beginning of period.
†Average.
‡Includes period of illness.

daily. The diet was increased by 500 calories to 70 per cent above the average, and a further gain of 1.2 kg. was achieved in five days. The fat diet of the same caloric value was then substituted for the dextrose diet, and the weight remained stationary. An increase of 250 calories daily (180 per cent of average caloric intake) resulted in steady gains which were maintained until the end of the experiment, at which time the child was from 2 to 3 per cent above average weight for her height.

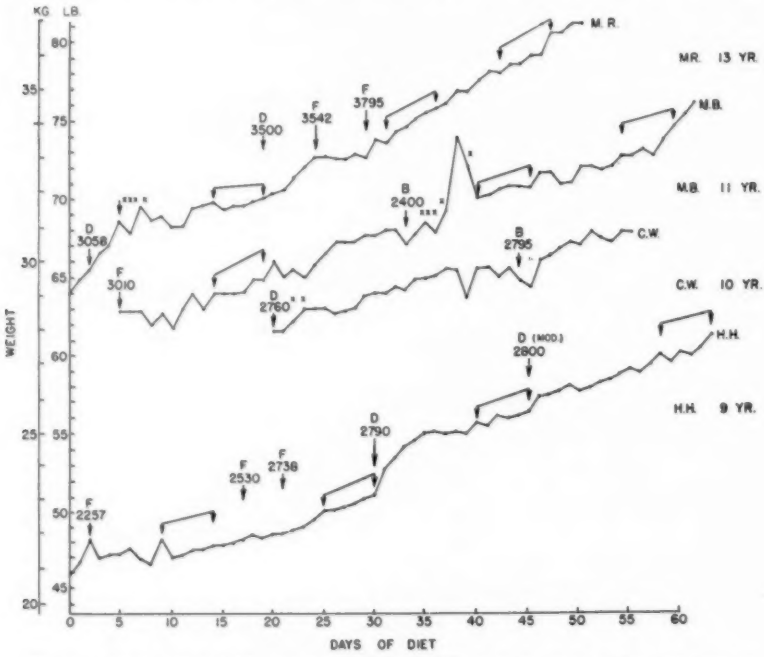


Chart 1.—Gains in weight of undernourished children in relation to diet. The letters indicate type of diet: *N*, normal; *D*, dextrose; *F*, fat. The figures below the letters show the caloric intake; *xxx* above the curve indicates periods of febrile illness. The bars indicate periods of metabolic study. To the right of the chart, the child's initials and age are placed at the level showing average weight for age and height.

The boy S. H., 13 years of age and about the same size as M. R., was given first the fat diet with an energy content 60 per cent above average intake. No weight gain occurred until the diet was increased by 500 calories, making a total intake 80 per cent above average. He was then fed up to the limit of his appetite, which was not reached until he was ingesting double the customary intake. The resulting weight gain was rapid, 1.3 kg. in five days. The dextrose diet was then substituted for the fat diet in isocaloric amount. The additional bulk was an obstacle at first, but after three days the entire diet was eaten. Despite the lowered energy intake of the first three days, the rapid weight gains were maintained and for the first few days of ingestion of the entire diet they were exceeded. After ten days the diet was decreased by

500 calories, with resulting weight loss. On resumption of the higher diet, weight gain continued. Nine days after resuming the high diet the intake was again lowered by 500 calories daily; the weight gain continued even though average weight for height had been attained. The rapid decrease in weight after the first reduction in diet was evidence that considerable weight was still due to water. The continued gain after the second decrease in food intake indicated that within nine days the water had been replaced by tissue gains. Further evidence for this inference is presented subsequently.

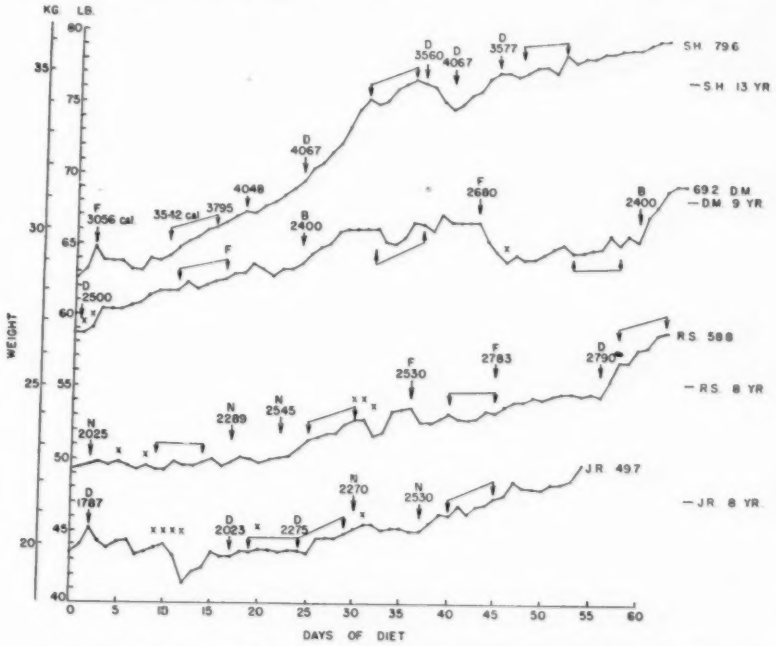


Chart 2.—Gains in weight of undernourished children. Symbols as in Chart 1.

H. H., a severely malnourished boy of 9 years, was given the fat diet in an amount 40 per cent above the average intake for his age. No consistent nor rapid weight gain ensued until the food intake was increased to 80 per cent above the average. Changing to the dextrose diet at the same caloric level resulted in large weight gains averaging 340 Gm. daily for five days, after which time the weight gain paralleled that of the previous diet. It is worthy of note that the rapid early weight gains, although undoubtedly due to water retention, were not lost later, but were converted into tissue gains without a period of stationary weight. The psychologic effect of such gains is of real value.

The weight curves of the younger children (J. R., 7 years, dextrose diet, and R. S., 8 years, normal diet) show that rapid gains were not achieved until the caloric intake was 50 per cent or more above the

average. The dextrose diet at 150 per cent of average caloric intake resulted in definite weight gains for J. R., but the subsequent ingestion of the normal diet at 170 per cent of average intake permitted somewhat less gain in a similar period of time. Similarly, with the child R. S. the normal diet had to be increased to 165 per cent of average caloric intake to produce consistent gains. The same total intake from the subsequently administered fat diet (by this time 160 per cent of the average) resulted in slight weight loss. Increase of intake to 165 per cent of the average resulted in a gain of 800 Gm. in nine days and stationary weight for the succeeding four days. The same caloric intake given as the dextrose diet resulted in the usual sharp increase in weight, even though the child's weight was little below normal when this diet was started.

This series of experiments demonstrated that weight gains were larger and more consistent with the dextrose diet than with either of the other two. The large early gains, which were ascribed to water retention, were not subsequently lost. Retention studies, discussed subsequently, indicated that the excess water was rapidly replaced by tissue.

In the second series of experiments a fourth diet was introduced, substituting 100 Gm. of ripe banana for each 20 Gm. of dextrose. As the dextrose diet had contained little roughage and much water, the question arose as to whether such a diet could still produce weight gains if the water content were lowered and the content of indigestible material increased.

Two children from relief rolls, D. M., 9 years, and C. W., 10 years of age, were admitted for study. They were first given the dextrose diet in amounts from 35 to 40 per cent above the average caloric intakes for their ages. Each child gained weight consistently. They were then given the banana diet, and weight gains continued at approximately the same rate. At this time, C. W. left the hospital. The other child, D. M., was given the fat diet with a caloric intake 10 per cent higher than that of the banana diet. A sharp loss in weight resulted, with a succeeding slow gain. A return to the banana diet at a lower caloric level, 110 per cent of normal, quickly restored the lost weight.

The 11-year-old girl, M. B., with atrophic arthritis in an inactive stage, gained weight satisfactorily for four weeks while ingesting the fat diet with a caloric intake 60 per cent above the average. Twice the preceding weight gain was achieved during the next four weeks when the banana diet was ingested in a quantity only 10 per cent above the average caloric intake, despite the fact that the child attained average weight during the first week of the diet.

The second series of experiments thus confirmed the results of the first series and demonstrated that fluid intake and bulk of intestinal content were not of major importance in determining weight gains.

A study of the relative caloric intake of these children in relation to weight gain provides interesting data (Table III). It will be observed that, when less than 150 per cent of the normal caloric intake was given, daily weight gain tended to be poor. For the two children fed the banana diet, and in five of the 8 studies with the dextrose diet, weight gain exceeded 75 Gm. daily, or a gain averaging over one pound a week. Weight gains were consistently good for all children given the dextrose diets in amounts over 150 per cent of the average caloric intake. Gains were neither consistent nor large for the fat diet until more than 175 per cent of normal caloric intake had been reached. Thus, the less efficient utilization of this diet, together with its high satiety value, more than counteracts the advantage of its small bulk. The few studies with banana were insufficient to draw definite conclusions in this first series, but encouraged further experiments with this diet. The dextrose diet appeared definitely superior to the normal diet in producing weight gains.

TABLE III

| NUMBER OF SUBJECTS | NUMBER OF STUDIES | TYPE OF DIET | CALORIC INTAKE AS % OF NORMAL | | DAILY WEIGHT GAIN (GM.) | |
|---|---|---|---|---|---|---|
| | | | RANGE | AVERAGE | RANGE | AVERAGE |
| 2 | 3 | N | 130-150 | 140 | 0-20 | 11* |
| 2 | 2 | F | 130-140 | 135 | −12-7 | −2 |
| 5 | 8 | D | 110-150 | 136 | −20-100 | 62† |
| 2 | 3 | B | 110-135 | 119 | 91-300 | 177 |
| 2 | 2 | N | 150-175 | 168 | 45-55 | 50 |
| 5 | 6 | F | 150-175 | 163 | −52-68 | 15 |
| 3 | 3 | D | 150-175 | 166 | 139-330 | 223 |
| 3 | 5 | F | 175-200 | 185 | 137-340 | 192 |
| 1 | 2 | D | 175-200 | 185 | 155-250 | 202 |

*Includes one period of illness.
†Includes three periods of illness.

The study was then extended to include children under 6 years of age (Chart 3). These children, in general, did not make as satisfactory subjects as did the older children. The results, however, illustrate the principles involved. Because of the poorer weight gains when high fat was ingested, the fat diet was not given to the young children.

Two of the younger group, R. D., a behavior problem, and J. W., who had chronic infection, were brought to the hospital primarily because of habitual emesis. Psychic factors were paramount in each. Because of emesis and frequent food refusals, caloric intakes could not always be determined accurately. Both children had low-grade fever from upper respiratory infection during approximately one-third of the period studied. Despite these drawbacks, both children gained weight when given the dextrose or banana diet, although R. D. had failed to gain when ingesting the normal diet.

A third child, R. Ws., could be studied for only nine days. During this time he was given the banana diet in an amount only 10 per cent

above average calorie intake; he gained 600 Gm. The dietary therapy was continued at home, and the child's weight eventually became normal.

The three children with celiac disease made excellent weight gains with both the dextrose and the banana diets. It is worthy of note that several incidents of upper respiratory infection with periods of elevated temperature of three to four days' duration did not occasion any marked weight loss in these children.

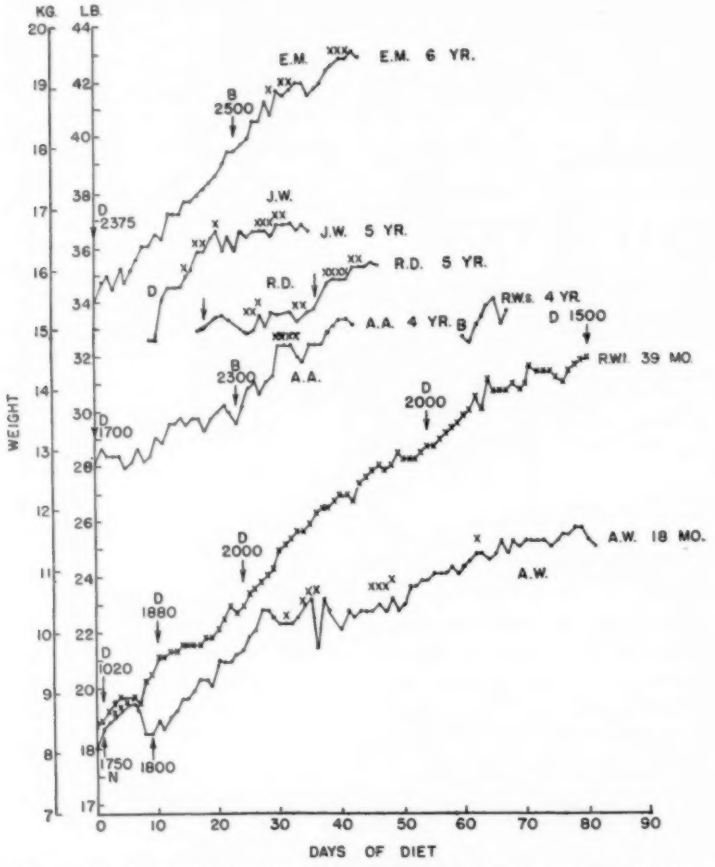


Chart 3.—Gains in weight of young undernourished children in relation to diet. *B*, banana diet; *D*, dextrose diet; other symbols as in Chart 1.

The weight curve of R. Wt., a 3-year-old child with chronic diarrhea and severe malnutrition, whose recovery was reported in detail elsewhere,[7] is again shown in order to demonstrate that large gains in weight can be maintained over a period of months without setback when a diet low in fat and complex carbohydrates is fed. (See Chart 4.)

The findings confirm the general observation that in severe malnutrition weight gain is dependent upon calorie intake. The weight gain was seldom satisfactory until the calorie intake was well above the average for a well-nourished child.

### GAINS IN HEIGHT

Among the older children nothing striking was observed in relation to growth in height. S. H. grew 2 cm. during the last twenty days of the study; the other children increased in height from 0.5 to 1.0 cm. each during the period of study.

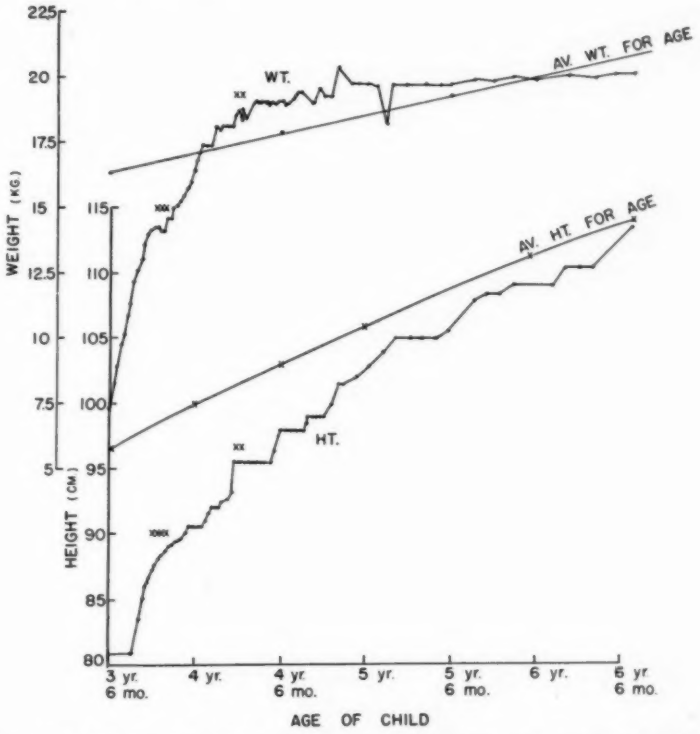


Chart 4.—Weight and height gains of R. Wt. during recovery from severe malnutrition.

It is in younger children that stunting from malnutrition is most often observed. In the younger group of this study, gain in height was often as spectacular as gain in weight. Four of the group (A. W., R. Wt., A. A., and E.M.) were definitely stunted at the beginning of the experiment. Two of the children (A. A. and E.M.) began to show gains in height almost as soon as in weight. A. A. grew 5 cm. during the six weeks of study, yet was still 6.6 cm. shorter than his normal twin brother. E. M. grew 4 cm. in six weeks and was then 4 cm.

shorter than his normal twin sister. Two other children (A. W. and R. Wt.) showed no growth in height until a considerable gain in weight had been achieved. Linear growth, once started, was very rapid for a period, which in turn might be followed by a period when the growth was slow. The youngest child (A. W.) grew 2.6 cm. during the eighty-two days of the study. Over one-half of this gain (1.5 cm.) was achieved during the last month. The rapid growth of R. Wt. is shown in Chart 4; no gain in height occurred until after six weeks of consistent weight gain. The child then increased 7 cm. in length during the next six weeks. This period of rapid growth was followed by several months of slower but steady growth, so that after eight months of treatment, the child was 14 cm. taller, having grown 11 cm. more than expected for a child of his age. At this time he was only 7 cm. below average height, and his weight was slightly above average for his age. Growth in height then slowed and became more intermittent, with short periods of rapid growth succeeded by longer periods of no growth. Average height for age was not achieved until the child was 7 years old, three and one-half years after treatment began. During these three and one-half years his height increased 32 cm., at the following rate: 17 cm. the first year; 7 cm. the second; 5.5 cm. the third; and 2.5 cm. the last six months. Average rates of gain for these ages are approximately 5, 5, 4.25, and 2.25 cm., respectively. Thus, the nearer the child approached normal height, the slower his rate of gain became.

### RETENTION DATA

As rapid gain in weight was the primary goal of the experiment, equivalence of intake of nitrogen and minerals in the three types of diet was sacrificed in favor of greater palatability. In order to provide sufficient calories in diets free from fat and complex carbohydrate, it was necessary to include a larger amount of protein. It was presumed that much of the extra protein would be burned for energy, offsetting in part the disparity in nitrogen intake among the diets. The additional protein was given largely in the form of skimmed milk or milk products; therefore, the intake of calcium and phosphorus, as well as of nitrogen, was higher for the children given the dextrose and banana diets than for those receiving the fat and normal diets. The retention data are given in Table IV.

Charts 5 to 7, inclusive, show the relation between intake and retention of calcium, phosphorus, and nitrogen per kilogram of body weight for those children over 6 years of age; charts 8 to 10, inclusive, report the same type of data for the children under 6 years of age.

Calcium and phosphorus retention in the group of older children increased steadily with increasing intake of these elements. Uniformly the dextrose and banana diets permitted the larger intake, and therefore the larger retention, of these elements. Even with the largest intake, however, occasional periods of loss of calcium from the body

were observed. Additional vitamin D was not given. These findings point to the desirability of such an addition. The average retention of calcium for intake was somewhat below that of normal children of

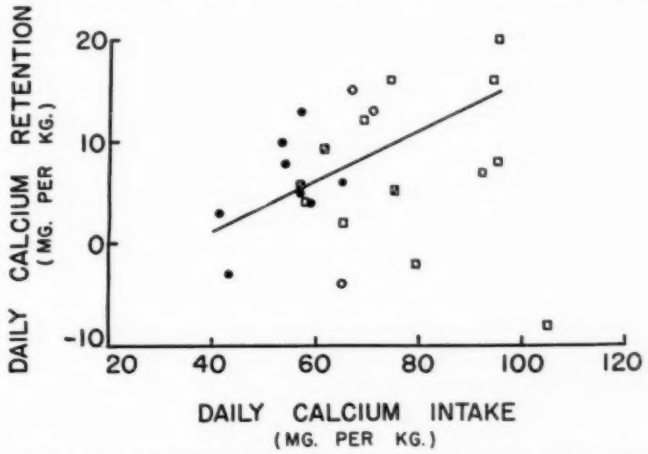


Chart 5.—Retention of calcium by older undernourished children in relation to diet and intake. The type of diet is shown by the type of symbol: solid dots represent retention from the fat diet; circles, the normal diet; open squares, the dextrose diet; and squares with diagonal, the banana diet.

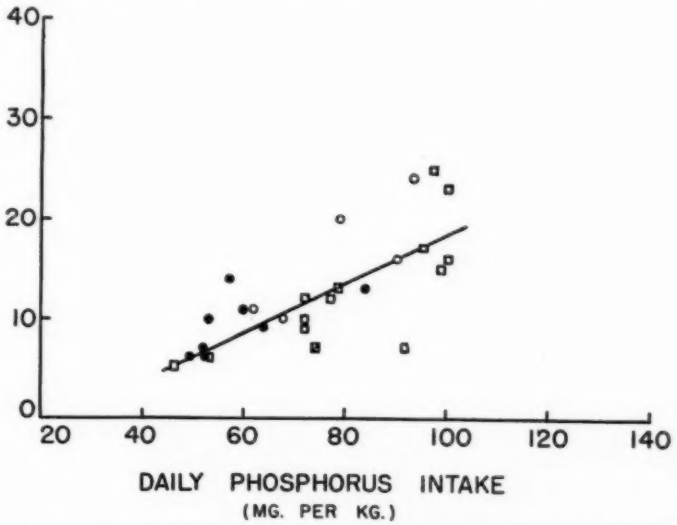


Chart 6.—Retention of phosphorus by older undernourished children in relation to diet and intake. Symbols as in Chart 5.

these ages. Apparently, undernutrition, like illness, decreases the efficiency of the gastrointestinal tract for absorbing calcium. Phosphorus retention tended to parallel calcium retention at a slightly

TABLE IV

INTAKE AND RETENTION OF CALCIUM, PHOSPHORUS, AND NITROGEN IN MILLIGRAMS PER KILOGRAM DAILY, AND TOTAL DAILY EXCRETION OF CREATININE OF UNDERNOURISHED CHILDREN

| NAME AND DISEASE | AGE (YR.) | DATE | WEIGHT (KG.) | DIET* | CALCIUM | | PHOSPHORUS | | NITROGEN | | CREATININE EXCRETION, MG. DAILY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | INTAKE | RETENTION | INTAKE | RETENTION | INTAKE | RETENTION | |
| *I. Children Under 6 Years of Age* | | | | | | | | | | | |
| A. W. | 1½ | 12/10 | 8.6 | N | 159 | −15 | 152 | 16 | 696 | 249 | 71 |
| Celiac | | 1/6 | 10.3 | B | 139 | 47 | 146 | 41 | 1263 | 394 | 72 |
| | | 2/17 | 11.4 | B | 109 | 81 | 81 | 40 | 892 | 507 | 100 |
| R. Wt.† | 3½ | 5/23 | 9.7 | D | 168 | 62 | 194 | 66 | 1450 | 486 | 96 |
| Chronic | | 7/6 | 13.3 | D | 156 | 68 | 175 | 69 | 1340 | 429 | 191 |
| diarrhea | | 8/25 | 14.1 | D | 124 | 50 | 127 | 40 | 1050 | 338 | 196 |
| A. A. | 4 | 9/29 | 13.4 | D | 121 | 43 | 125 | 23 | 1101 | 160 | 201 |
| Celiac | | 10/7 | 13.7 | D | 119 | 35 | 122 | 14 | 1088 | 106 | 230 |
| | | 10/25 | 14.7 | B | 114 | 41 | 119 | 20 | 1080 | 131 | --- |
| | | 11/1 | 15.1 | B | 111 | 15 | 116 | 20 | 1051 | 97 | 249 |
| R. Ws. | 4 | 7/7 | 15.2 | B | 91 | −10 | 115 | 55 | 838 | 147 | 300 |
| R. D. | 5 | 10/25 | 15.2 | N | 93 | 30 | 80 | 18 | 632 | 97 | 265 |
| E. M. | 6 | 9/29 | 16.9 | D | 153 | 58 | 135 | 32 | 1182 | 181 | 269 |
| Celiac | | 10/7 | 17.7 | D | 146 | 59 | 128 | 34 | 1113 | 215 | 271 |
| | | 10/20 | 19.0 | B | 139 | 61 | 131 | 34 | 1112 | 193 | --- |
| | | 10/25 | 19.2 | B | 131 | 39 | 124 | 23 | 1081 | 140 | 290 |
| | | 11/1 | 19.5 | B | 131 | 68 | 124 | 31 | 1066 | 160 | 296 |

*II. Children Over 6 Years of Age*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| J. R. | 7 | 10/5 | 20.4 | D | 95 | 8 | 92 | 7 | 706 | 54 | 439 |
| | | 10/9 | 20.4 | D | 105 | −8 | 100 | 16 | 820 | 141 | 474 |
| | | 10/25 | 21.5 | N | 65 | −4 | 90 | 16 | 725 | 84 | 565 |
| | | 11/18 | 22.4 | N‡ | 86 | 27 | 93 | 24 | 735 | 189 | 564 |
| R. S. | 8 | 9/24 | 22.5 | N | 67 | 15 | 68 | 10 | 550 | 57 | 482 |
| | | 10/11 | 23.9 | N | 69 | 13 | 79 | 20 | 673 | 120 | 524 |
| | | 10/25 | 24.0 | F | 43 | −3 | 52 | 6 | 423 | 23 | 531 |
| | | 11/13 | 24.7 | D | 79 | −2 | 95 | 17 | 840 | 61 | 550 |
| H. H. | 9 | 9/25 | 21.6 | F | 59 | 4 | 49 | 6 | 536 | 123 | 456 |
| | | 10/11 | 23.1 | F | 57 | 4 | 60 | 11 | 514 | 92 | 542 |
| | | 10/26 | 25.6 | D | 92 | 7 | 99 | 15 | 760 | 52 | 616 |
| | | 11/14 | 27.4 | D | 58 | 4 | 72 | 10 | 592 | 79 | 655 |
| D. M. | 9 | 2/26 | 28.4 | D | 41 | 3 | 46 | 5 | 396 | 45 | --- |
| | | 3/18 | 30.1 | B | 69 | 12 | 77 | 12 | 708 | 99 | 650 |
| | | 4/8 | 29.5 | F | 65 | 5 | 82 | 13 | 718 | 118 | 655 |
| M. B. | 11 | 3/10 | 29.4 | F | 54 | 8 | 52 | 7 | 431 | 50 | 645 |
| Atrophic arthritis, inactive | | 4/5 | 32.0 | B | 61 | 9 | 79 | 13 | 670 | 124 | --- |
| | | 4/19 | 33.8 | B | 57 | 5 | 74 | 7 | 645 | 73 | 678 |
| M. R. | 12 | 9/29 | 31.8 | D | 74 | 16 | 72 | 12 | 555 | 119 | 651 |
| | | 10/17 | 34.3 | F | 57 | 13 | 57 | 14 | 494 | 150 | 675 |
| | | 10/31 | 36.9 | F | 53 | 10 | 53 | 10 | 455 | 97 | 685 |
| S. H. | 13 | 9/25 | 29.8 | F | 65 | 6 | 62 | 9 | 495 | 75 | 748 |
| | | 10/16 | 34.6 | D | 94 | 16 | 100 | 23 | 860 | 259 | 840 |
| | | 11/2 | 35.0 | D | 95 | 20 | 97 | 25 | 825 | 192 | --- |
| | | 11/13 | 35.2 | D | 65 | 2 | 72 | 9 | 680 | 58 | 932 |

*Diets listed as in Table I.
†Data reported previously.[7]
‡Post-tonsillectomy period.

higher level. As calcium retention appears to be depressed in malnutrition, it would seem safer to supply an excess of this element and to provide means of ensuring its utilization.

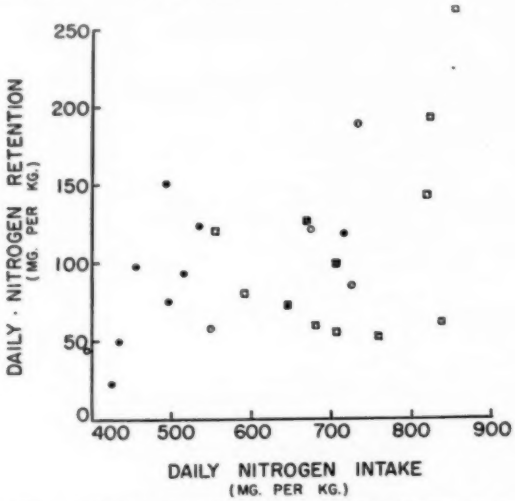


Chart 7.—Retention of nitrogen by older undernourished children in relation to diet and intake. Symbols as in Chart 5.

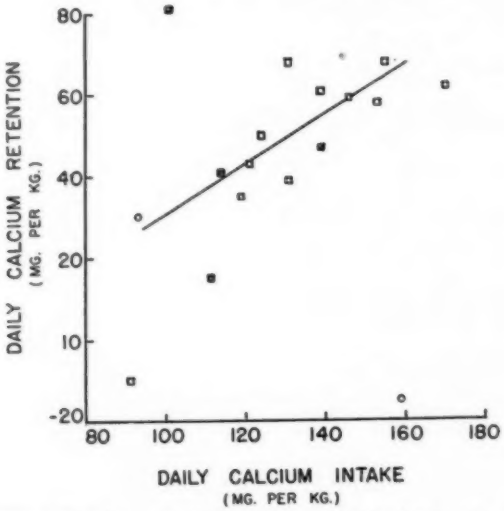


Chart 8.—Retention of calcium by young undernourished children in relation to diet and intake. Symbols as in Chart 5.

All children of the younger group were given additional vitamin D during the study. The calcium and phosphorus retention tended to follow the intake (Charts 8 and 9) as was observed in the older group.

The younger children, however, were more efficient in this respect, and only one period of calcium loss was observed. The average intake and retention per kilogram for both calcium and phosphorus are equivalent to those commonly observed in infancy and are much greater than those usual for healthy children of the ages represented by our study

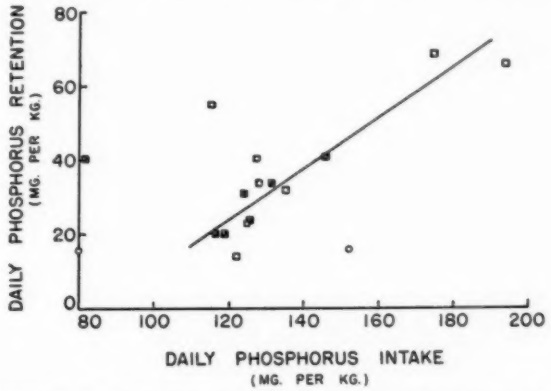


Chart 9.—Retention of phosphorus by young undernourished children in relation to diet and intake. Symbols as in Chart 5.

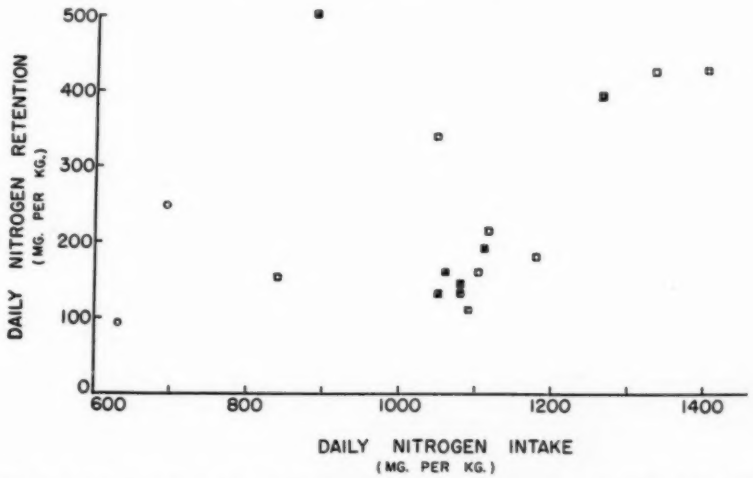


Chart 10.—Retention of nitrogen by young undernourished children in relation to diet and intake. Symbols as in Chart 5.

group. It seems probable that depletion of calcium stores occurred during the period of malnutrition; rapid replacement under adequate dietary management is shown to be possible. It is interesting to note that the average ratio of calcium to phosphorus retention was greater than 1 in the younger group and less than 1 in the older children who

did not receive additional vitamin D. A retention ratio greater than 1 is indicative of rapid deposition of mineral in bone; a ratio of less than 1 indicates rate of growth of soft tissues greater than that of bone.

The nitrogen retention of both groups of children (Charts 7 and 10) was consistently good when the intake was above 450 mg. per kilogram. The older children who were given the high fat diet showed a very consistent relation between intake and retention. These children apparently were not using protein for energy to any great extent.

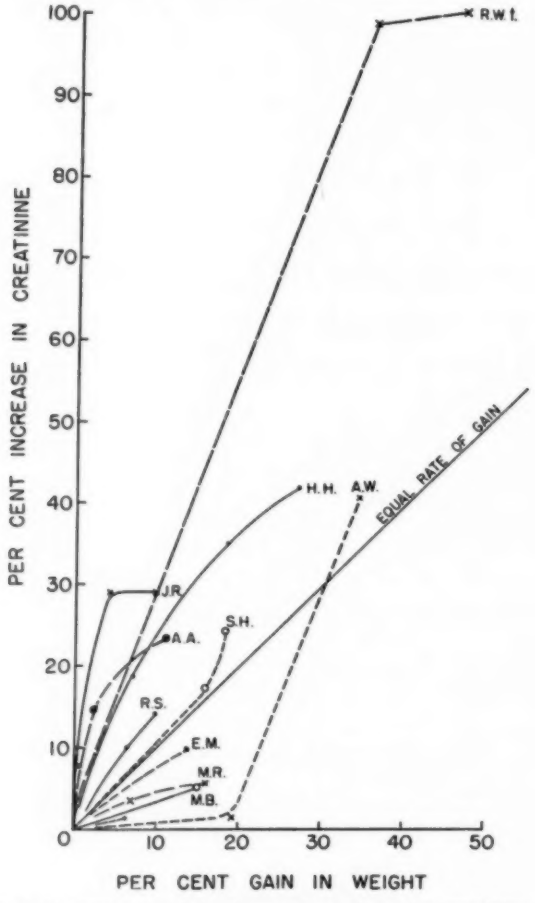


Chart 11.—Rate of increase in skeletal muscle, as shown by creatinine excretion, in relation to rate of gain in total body weight.

The wider range of retention values obtained with the dextrose and banana diets indicates that a variable amount of the dietary protein was used for energy. In no case was the amount needed for energy

sufficient to cause a poor retention. In fact, the average nitrogen retention was unusually high for each age group. No evidence of any ill effect was observed in any child given the high protein diet.

### CREATININE EXCRETION

Excretion of creatinine in the urine was observed as a means of determining muscle growth. As judged by this criterion, the quantity of skeletal musculature increased rapidly during the periods of weight gain. For the group of older children, the rate of increase in musculature as shown by creatinine excretion is compared with the rate of increase in weight in Chart 11. It will be noted that four of the group of older children (H. H., S. H., J. R., and R. S.) showed a relative rate of gain in musculature greater than the rate of increase in weight. The child J. R. at first showed increase in muscle weight without any increase in total weight. In all these children replacement of fat or water by muscle tissue was apparently proceeding even during periods of rapid weight gain. Gains in musculature occurred with each of the diets given. Three of the children (D. M., M. B., and M. R.) showed a rate of gain in weight greater than that for musculature.

Of the younger group, four of the children were studied long enough for comparative data to be of value. Two of the children (R. Wt. and A. A.) showed from the beginning a greater rate of increase in muscle weight than of total weight. A third child (E. M.) gained muscle at a somewhat lower rate than that of gain in total body weight. The fourth child (A. W.) showed a gain of nearly 20 per cent in weight, with little or no gain in muscle; after this period, conditions seemed to be reversed and the rate of gain of musculature was far more rapid than that of gain in weight, so that at the end of the study, the child's weight had increased about 35 per cent and the skeletal muscle 41 per cent. This occurrence gives rise to speculation as to the final outcome of the muscle:body weight relationships of the four children whose gain in muscle was relatively less than the gain in total weight, none of whom showed a total weight gain of over 15 per cent. It is possible that a longer period of study would have shown a reversal of comparative rates of gain, with a final outcome similar to that of the child A. W. As the study stands, it seems that, with similar diets, some children tend to form muscle more rapidly than they deposit fat, while for other children, the reverse is true.

### OTHER FINDINGS

Dextrose tolerance curves were obtained with the group of older children. The data showed, as expected, that the higher fat intake caused delayed return of blood sugar to normal and that the high glucose intake caused a sharp fall to normal. In no case was the blood

sugar curve abnormally high, nor was sugar observed in the urine of any child. One child of the group (H. H.) given the fat diet continuously excreted acetone in the urine, as shown by the Rothera test.

## SUMMARY

Four types of diets were used in a study of weight gain in undernourished children, viz., the customary diet used in this hospital, designated the "normal" diet, a diet richer in fat called the "fat" diet, and a diet low in both fat and complex carbohydrates, containing its calories as protein and dextrose, the "dextrose" diet. In the fourth diet ripe bananas were substituted for an equivalent amount of dextrose.

Weight gains were more rapid with the dextrose and banana diets than with either of the other two. Consistent weight gains were obtained with the dextrose and banana diets at lower caloric intake than with the other diets. The fat diet necessitated largest caloric intake in order to maintain consistent weight gain.

The rapid early gains in weight observed with banana and dextrose diets, presumably due in large part to water retention, were not subsequently lost, but were apparently replaced by tissue gains without an intervening period of slow or no gain. The psychologic effect of such gains is apparent.

The studies of retention of calcium, phosphorus, and nitrogen confirm the results of the studies of the weight gain and show that diets made up of protein and simple carbohydrates provide intake levels of these substances such that good body tissue can be built rapidly. These studies provide proof that the spectacular weight gains observed are due primarily to sound tissue growth, and that the resulting normal weight is an indication of normal body composition and not due to inordinate amounts of fat or water.

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# VALIDITY OF ETIOLOGICAL DIAGNOSIS OF PNEUMONIA IN CHILDREN BY RAPID TYPING FROM NASOPHARYNGEAL MUCUS

H. E. Alexander, M.D., H. R. Craig, M.D.,
R. G. Shirley, M.D., and C. Ellis
New York, N. Y.

ACCURATE, rapid identification of the infectious agent is helpful in the chemotherapy of pneumonia and essential for the institution of serum treatment.

The present report deals with the results of direct typing from nasopharyngeal mucus, using the Neufeld reaction, and constitutes an attempt to estimate the dependability of the method. The preliminary findings of one year's experience at the Babies Hospital have already been reported;[1] subsequently, Hodes and his co-workers[2] used this method with success.

Felty and Heatley[3] first reported close agreement between the organisms recovered from the nose and the sputum in a group of sixteen adults. Baker[4] showed that in the early stage of pneumonia due to pneumococcus, Type I, the organisms were quickly recovered from nasal swabs by means of mouse inoculation. Poole and Fousek[5] reported a group of forty-eight cases in which typing was performed from nasopharyngeal mucus obtained with a swab carried on a wooden applicator. This material was planted in 1 c.c. of broth; after incubation for a few hours typing was attempted. In a small number of cases where confirmatory evidence from other sources was available, there was fairly good agreement between the results of the two or more cultures. With similar material secured by means of a rubber catheter and typed directly by the Neufeld method, Auger[6] obtained excellent results in 400 cases. No figures were presented, but agreement between the type of pneumococcus from the nasal mucus and that from other biologic fluids significant in establishing the etiology was reported to be 90 per cent.

There is general agreement that nasopharyngeal mucus is superior for typing to material obtained on pharyngeal swabs. Objective evidence concerning the degree of correlation between the findings from this source and the organisms causing the lesion in the lung is limited. Blacklock and Guthrie,[7] Kereszturi and Hauptman,[8] and Bullowa and Greenbaum[9] have compared the results of culture of material obtained by lung puncture and that procured with pharyngeal swabs.

In starting our own inquiry, three different methods for obtaining nasopharyngeal mucus for typing were investigated. These were as

From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University.

follows: (1) A small cotton swab on a copper wire* applicator was passed back through the nose to the pharyngeal wall; (2) a long platinum wire with a small loop at its end was similarly introduced; (3) a cotton swab on a wire applicator bent to an angle of about 100° was passed through the mouth to the nasopharyngeal wall. The first method was chosen for the present study of 377 cases of pneumonia because of its ease of application, and because, unlike the platinum loop, it yielded a quantity of material adequate for direct typing. The swab was allowed to remain in position for a brief period to collect mucus. It was found to be important to allow time for the swab to become moistened, after introduction into the nares, before applying a twirling, gentle, backward pressure until the posterior wall was encountered. On withdrawal after an interval of fifteen seconds, the swab was placed in 0.2 c.c. of pneumococcus broth and sent immediately to the laboratory where the adherent mucus was freed before the swab was removed and discarded. The broth was then used to prepare poured plates and to inoculate a blood agar plate and 3 c.c. of blood broth in a tube before being utilized for direct typing by the Neufeld method. When direct typing failed, the blood broth, after a few hours' incubation, was examined by the same procedure. The early preparation of poured plates was in order to save time in the detection of *Streptococcus hemolyticus.*

Table I shows the results of direct typing from the 0.2-c.c. suspension of mucus, the typing from young cultures in blood broth when the direct method was unsuccessful, and also lists the results of those cultures not identified in twelve hours. The average incubation time required for broth cultures to reach a growth phase suitable for typing was from three to five hours. A small number required from twelve to eighteen hours. Emphasis should be placed on the fact that the ease and speed with which the direct typing can be accomplished depend upon whether the mucus has been obtained from the nasopharynx or the nares. If the above procedure is followed carefully, the organism can be typed accurately in nearly 100 per cent of cases of pneumococcus pneumonia within a half hour after the material has reached the laboratory. In this study, although the large number of persons who collected the specimens caused variation in technique, 82 per cent of the cases were typed directly from the 0.2-c.c. suspensions of mucus within a half hour period and 18 per cent from the young blood broth culture. In less than 2 per cent of the cases of pneumococcus pneumonia rapid typing by these two methods was unsuccessful. Taking all varieties of causative organisms together, 81 per cent were identified from nasopharyngeal mucus by the rapid method. Of the 19 per cent which were diagnosed by more time-consuming cultural methods, 55 per cent were due to *Streptococcus hemolyticus.* Of the

*Stiff copper wire 1 mm. in diameter was cut into 5½-inch lengths. One end of each piece was looped over for ½ inch for ease in handling, and the other end was abraded to aid adherence of the cotton swab which was made as small as possible.

TABLE I

A. 317 CASES IN WHICH THE ORGANISM WAS IDENTIFIED BY RAPID METHODS

| NUMBER OF CASES | ETIOLOGICAL AGENT | METHOD | TIME REQUIRED TO COMPLETE IDENTIFICATION |
|---|---|---|---|
| 255 | Pneumococcus | Directly from nasal mucus | Approximately 30 minutes |
| 59 | Pneumococcus | Indirectly from blood broth culture of nasal mucus | 3 to 12 hours |
| 3 | *H. influenzae* | Directly from nasal mucus | Approximately 30 minutes |

B. 60 CASES IN WHICH ORGANISM WAS NOT IDENTIFIED IN TWELVE HOURS

| NUMBER OF CASES | ETIOLOGICAL AGENT | SOURCE OF ORGANISM | REMARKS |
|---|---|---|---|
| 34 | *Streptococcus hemolyticus* | Predominating in nasopharyngeal cultures | |
| 5 | Nontypable pneumococci | Predominating in nasopharyngeal cultures | |
| 5 | Nontypable *H. influenzae* | Predominating in nasopharyngeal cultures | |
| 5 | *Staphylococcus aureus hemolyticus* | Predominating in nasopharyngeal cultures | With confirmatory evidence from other sources |
| 6 | *Staphylococcus aureus hemolyticus* | Predominating in nasopharyngeal cultures | With no confirmatory evidence, but absence of other pathogens |
| 2 | Pneumococcus | Predominating in nasopharyngeal cultures | Typable only after several transfers |
| 1 | Pneumococcus, Type I | From blood cultures | Only source |
| 2 | No significant pathogens | In nasopharyngeal cultures | |

Of 377 cases, 84 per cent (317) were identified in less than twelve hours; 68 per cent (258) were identified in approximately thirty minutes; 81 per cent were identified by rapid method; 19 per cent were identified by cultural methods, and of these, 55 per cent were due to *Streptococcus hemolyticus*.

TABLE II

EVIDENCE CONCERNING THE DIAGNOSTIC SIGNIFICANCE OF THE ORGANISM IDENTIFIED BY RAPID TYPING IN 317 CASES

| | NUMBER OF CASES | ETIOLOGICAL AGENT | SOURCE OF CONFIRMATORY CULTURES | ADDITIONAL VARIETIES OF ORGANISM PRESENT |
|---|---|---|---|---|
| Identical organism from other source | 24 | Pneumococcus | Lung puncture | None |
| | 12 | Pneumococcus | Blood culture | None |
| | 5 | Pneumococcus | Pleural fluid | None |
| | 1 | Pneumococcus | Post-mortem findings | *Staphylococcus aureus hemolyticus* |
| | 2 | *H. influenzae*, Type b | Blood culture | None |
| | 1 | *H. influenzae*, Type b | Lung puncture | None |
| Different organism from other source | 1 | *Streptococcus hemolyticus* | Pleural fluid | Pneumococcus* |
| | 1 | *Staphylococcus aureus hemolyticus* | Two blood cultures | Pneumococcus* |
| No organism from other source | 69 | | Lung puncture | |

*By direct typing from nasopharyngeal mucus.

Of forty-five cases, 95 per cent (forty-three) were diagnosed correctly by rapid typing.

258 cases in which typing was accomplished directly from the nasopharyngeal mucus by the Neufeld method within thirty minutes, three were shown by the use of diagnostic rabbit antisera to be Type b *H. influenzae*. The procedure is identical with that used for pneumococci, with the substitution of specific *H. influenzae*, Types a and b, diagnostic sera.[10] The morphologic characteristics of *H. influenzae* in mucus are often indistinguishable from those of the pneumococcus when they are stained by methylene blue in the Neufeld preparation. It has been our custom routinely to set up the mucus suspension with *H. influenzae* antisera whenever a clear-cut answer is not obtained by direct Neufeld typing for pneumococci.

Table II lists the evidence available for evaluating the diagnostic accuracy of this rapid method of typing. As in all reported series, it is apparent that the evidence is limited. However, in the forty-five cases in which information is available, forty-three, or 95 per cent, were diagnosed correctly by rapid typing. The two exceptions concerned cases of pneumonia, one due to *Staphylococcus aureus hemolyticus* and the other to *Streptococcus hemolyticus*.

Early diagnosis of staphylococcus pneumonia constitutes the most difficult problem in all types of pneumonia. Unless a bacteriemia is present or empyema develops or the organism is grown from lung puncture, it is impossible to assess the significance of staphylococcus in the upper respiratory tract of those patients who recover, even when it is the predominating organism and other potential pathogens are absent. Even within the group of very young infants, in whom staphylococcus pneumonia is most prevalent, our limited experience is similar to that of Hallman[11] with older children. Hallman demonstrated that pathogenic staphylococcus is recovered from the upper respiratory tract with such frequency in normal children that its presence is of no diagnostic value. It is our plan to study such patients by the precipitin method of Julianelle and Hartman[12] and by lung punctures, using cultures of the nasopharyngeal mucus to select the patients.

TABLE III

RESULTS OF LUNG PUNCTURE

Of 98 lung punctures performed:
- 24 yielded pneumococcus
- 1 yielded *Streptococcus hemolyticus*
- 1 yielded *Staphylococcus aureus hemolyticus*
- 1 yielded *H. influenzae*, Type b
- 71 yielded no growth

Types cultured from lung puncture material were:

| | |
|---|---|
| Type XIV—11 cases | Type VI—1 case |
| Type I— 3 cases | Type VII—1 case |
| Type V— 3 cases | Type XI—1 case |
| Type II— 1 case | Type XV—1 case |
| Type III— 1 case | Type XIX—1 case |

Table III records the results of ninety-eight lung punctures. Like other reports of series of lung punctures, about two-thirds of the cul-

tures of the aspirated material yielded no growth. Of the twenty-four cases from which pneumococci were isolated, Type XIV was grown in eleven instances, that is, in 45 per cent of the positive cultures.

In the ninety-eight patients on whom lung puncture was performed, pneumothorax ensued twice. Recovery was uneventful within a ten-day period in both instances. There were no cases of empyema among these ninety-eight patients.

## SUMMARY

Nasopharyngeal mucus obtained through the nares and emulsified in 0.2 c.c. of pneumococcus broth serves as excellent material for direct typing of pneumococci and *H. influenzae* by the Neufeld method. Cultures of this material show a striking predominance of the etiological agent.

Three hundred and seventy-seven patients have been studied by this method: 317 cases, or 84 per cent, were diagnosed in less than twelve hours; 258 cases, or 68 per cent, were diagnosed in thirty minutes; 60 cases showed negative results in twelve hours, but within a twenty-four-hour period, 55 per cent of these showed a predominance of *Streptococcus hemolyticus* by culture.

Establishment of the etiological agent by the method outlined has been satisfactory even when carried out by a number of observers and in most instances upon one specimen of nasopharyngeal mucus.

Twenty-seven of the ninety-eight lung punctures yielded positive cultures. The organisms isolated are listed. There were no instances of empyema following lung puncture. Two patients developed pneumothorax subsequent to lung puncture, but both recovered uneventfully within a ten-day period.

The objective evidence available in forty-five cases showed confirmation in forty-three, indicating 95 per cent agreement.

The experience with lung puncture indicates that it is a relatively harmless procedure.

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# OBESITY IN CHILDHOOD AND ENDOCRINE TREATMENT

HILDE BRUCH, M.D.
NEW YORK, N. Y.

THE following cases are presented to show that obesity may develop in children receiving the very glandular products which are commonly considered to be of specific value in the treatment of obesity. Such cases are not isolated instances. These two patients were selected from a group of children with similar histories because they had been under clinical observation for some time before an endocrine disorder had been suspected or glandular treatment had been instituted. Data concerning weight development before the onset of obesity can be taken, therefore, from the clinic records. The available figures demonstrate that the abnormal gain in weight coincided with the administration of hormonal products. The chronologic concurrence suggests a causal connection. For the following report the material contained in the clinical records was supplemented by information concerning the attitude of the family to the patient. An effort was made to evaluate the effect of a diagnosis of endocrine disorder and of therapy with glandular products on the handling of the child by his parents. I am indebted to Mrs. Grace Touraine for her cooperation in obtaining this information on the family's reaction.

## CASE REPORTS

### CASE 1

*Medical History.*—The patient J. K. attended the Pediatric Department of Vanderbilt Clinic for the first time on Oct. 16, 1933, at the age of 5½ months. The chief complaint was a rash on the face of one week's duration. Although there was generalized eczema for a short time, the condition was not severe and had completely subsided when the boy was 8 months old. General progress was normal. There was, however, an inability to tolerate eggs. At 11 months of age the child reacted with sickness and repeated vomiting to a small amount of egg. After the age of infancy a number of visits were made to the Pediatric Clinic, chiefly for acute upper respiratory infections. There were no serious disorders during the whole period of observation. At the age of 6 years the patient was admitted to the Babies Hospital for tonsillectomy. The boy suffered from a slight postoperative hemorrhage which was not severe enough to warrant a transfusion.

*Sexual Maldevelopment and Therapy.*—At the time of the first visit to the clinic at 5½ months of age, it was noted that the genitals of the

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, and the Pediatric Division of the Vanderbilt Clinic, and the Babies Hospital.

This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

patient were poorly developed. Only the left testicle was descended, and the penis could be felt but not seen, a condition that was diagnosed as "concealed penis" (Fig. 1). The mother was not aware of any abnormality and stated that a circumcision had been performed at the age of 5 weeks. During the following months no change in the state of genital development was observed. At the age of 15 months the boy was sent to the Urological Clinic for an opinion as to the advisability of glandular therapy. At the first examination at the Urological Clinic neither testicle could be felt and the foreskin was found to be tight and adherent on one side. Roentgenologic examination of the thymus and sella turcica was requested; no abnormalities were discovered.

Fig. 1.—Genital development of J. K. at age of 6½ months.

Treatment with an anterior pituitary-like gonadotropic substance from pregnancy urine* was instituted. Small doses were given, starting with 0.1 c.c. which was to be increased by 0.1 c.c. at each injection until 1.0 c.c. was reached. The child reacted to the first injections with vomiting and irritability, so that the increase in dosage was slower than planned. Between July 30 and Sept. 7, 1934, the boy received 7.8 c.c. of follutein (975 R.U.) in fourteen injections, the last of which was 1 c.c. Following this amount of treatment, the penis became visible and increased in size, and both gonads could be palpated.

Glandular treatment was continued in a series of subsequent courses, the extent of which is indicated by the black areas at the bottom of Fig. 2. The amount given ranged between 1 and 2 c.c. and is indicated by the varying height of the black area. The frequency of administration varied. It was as high as three injections per week for several

*Follutein (E. R. Squibb and Sons) was the preparation used. The strength of follutein was 125 R. U. per cubic centimeter; after 1935, the strength was 100 R. U. per cubic centimeter.

months in succession in 1935, and as low as one injection every other week at later periods. All in all, the child received 138.3 c.c. follutein (14,975 R.U.) in ninety-eight injections. The family showed excellent cooperation; there is scarcely a broken appointment in the whole record. Except for the remarks about the severe reaction to the initial injections, no further mention is made of either the presence or absence of local or general reaction to the treatment.

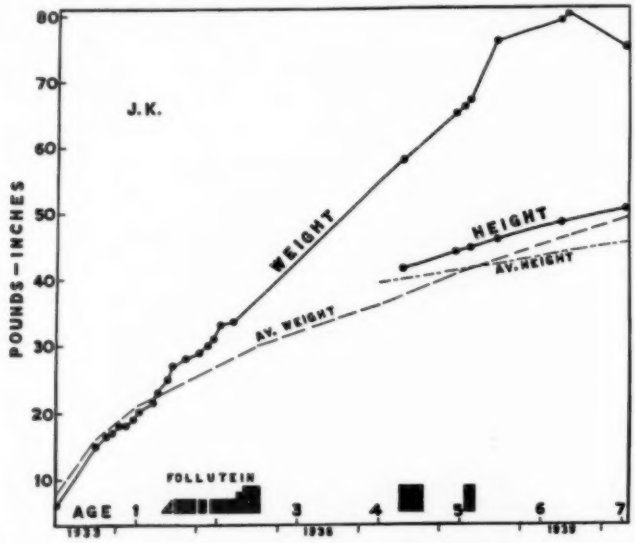


Fig. 2.—Height and weight development of J. K. (Case 1). Periods of treatment are indicated by the black areas; the different heights of the areas indicate the various amounts given. Age is given in years.

In reviewing the record it is difficult to form an opinion as to why treatment was continued so long and so extensively. It must be remembered that it was carried out at a time when practical experience with gonadotropic hormones in their effect on genital development of young children was quite limited. Apparently, the aim was to produce genital organs with complete descensus of both testicles. The difficulty of forming a valid opinion as to the state of descent of the testicles on the basis of a single examination is reflected in the variation between the findings of different examiners at different times. Thirty-eight examinations of the genitals of the now 7-year-old boy are recorded. There is little agreement between subsequent findings. Such a difference has already been illustrated by the fact that the left testicle had been felt repeatedly at pediatric examinations but could not be felt at the first urologic examination. The left testicle was generally palpated with greater ease than the right one, though a few descriptions record the opposite finding. The opinions as to the size and descent of the right testicle vary greatly. It was felt with certainty for the first time when

the patient was 16 months old. At subsequent examinations it was found in various positions of descent; on other occasions it could not be palpated. Such a statement was made as late as August, 1939, when the patient was 6 years and 4 months old. Mention is made of this great variability in the observations in order to illustrate how unreliable the examination and evaluation are in the case of a retractible testicle in a young child. It is doubtful whether at present such intensive treatment would be carried out over such a long period, as it had been observed that the right testicle did descend after administration of a small amount of hormone.

When the patient was seen in the Pediatric Obesity Clinic (from which the present report is being made) at the age of 6 years, the genitals appeared to be small for so large a child. Their true size was masked by accumulation of fat in the suprapubic region and could be appraised only after the fat masses were pushed back. The penis and scrotum were well formed, and both testicles were descended but retracted easily on examination.

*Physical Growth and Weight Development.*—The patient was born at full term, and his birth weight was 6 pounds. His progress was satisfactory, and his weight curve followed closely the average curve for normal infants (Fig. 2). Eruption of teeth, locomotion, and intellectual development were entirely normal. At the age of 15 months, just before glandular treatment was started, his weight coincided with the average curve. The subsequent figures for weight were recorded at the occasional visits to the Pediatric Clinic. That the increase in weight was abnormally large was not realized before the child was markedly obese at the age of 6 years. An endocrine diagnosis of "adiposogenital dystrophy" was made, and the patient was sent to the Pediatric Obesity Clinic for study and treatment.

The first measurement of the patient's height was recorded when he was 4 years and 2 months old. It was 41½ in., that is, about 2 in. above average for his age. His rate of statural growth during the following three years was somewhat greater than average.

At 6 years of age he was 49 in. tall and weighed 80 pounds, a weight excess of approximately 45 per cent for height and age.[1] His appearance and degree of obesity are illustrated in Fig. 3. There was a marked accumulation of fat in the abdomen, suprapubic region, and thighs, so that the genitals appeared to be imbedded in masses of fat. There was some accumulation of fat in the mammary region, but no glandular tissue could be felt. The face was round, the features were soft, and the expression was sluggish. A roentgenogram of the skull revealed no abnormality, and the skeletal maturation of the wrist (which was obtained later when the patient was 7 years old) was within normal limits. Examinations of urine and blood count were normal. The Mantoux test was negative. (It was repeated and was again negative one year later.)

The general picture which this patient offered, specifically the type of fat distribution, is not infrequently considered evidence of pituitary dysfunction, and administration of pituitary substance is recommended frequently for correction of the condition. The fact that the patient developed this so-called pituitary type of obesity while he was under intensive treatment with gonadotropic substance is striking evidence against the correctness of such a diagnosis.

Fig. 3.—J. K. (Case 1) at the age of 6 years. Note distribution and accumulation of fat, which has, however, no specific significance.

It was felt that a better understanding of the pathogenesis of the condition could be gained by a study of the whole life situation of the child, of his behavior and reaction, and of the family's attitude toward his disorder and his treatment.

*Behavior Aspects.*—The patient appeared to be a quiet, slow, and apprehensive boy. The mother stated that he always clung to her and

refused to play with other children. He would become hysterical at the thought of being left alone in the apartment. If the mother was called to the telephone after he was in bed, he would follow her in his night clothes. He was also dependent on her for his personal care; he was unable to dress without assistance, and she continued to bathe him. The mother described him as a nervous, restless, and irritable child, although there had been some improvement since the injections were discontinued. He had difficulty falling asleep, and there had been periods of marked disturbances in his sleep, with screaming out in the night. During the day he was tired, listless, and inactive. He would sit about quietly or play without vigor, keeping his playthings in perfect order even when he played with them. The mother, a fanatic on the matter of cleanliness and preservation of her furniture, stated rather proudly, "I brought him up to be that kind of a child." The patient was always a good eater and ate everything the mother gave him.

*Attitude of the Mother Toward the Patient and His Health.*—The mother was over 30 when she married, and the patient was an only child. She expressed regret that she had only one child and stated that economic reasons had been responsible for the small size of the family. In discussing her attitude toward him and his disorder she appeared to be an intelligent, matter-of-fact woman. She seemed to have accepted the child's condition and the long-continued treatment without undue concern—in retrospect, at least. She stated that the child was sick after each injection. There was always a local reaction, swelling, and redness. His temperature would rise to 102° F. If given food, he would be nauseated. The reaction would begin about three hours after the injection. He became sleepy and listless and was put to bed at 5 P.M. on the days of the treatment. He would sleep through the night like a drugged child, and on the following morning was completely recovered. Meals were designed on the next day to make up for the loss of nourishment. In retrospect, the mother realized that she had overfed him in her effort to compensate for his sickness. The perseverance of the mother in taking him three times weekly for treatment for such a long period, especially in the face of such severe reactions in the child, was commented upon. She simply stated, "I wanted him to be right," and expressed gratitude for the result. She was concerned about his overweight, especially his enormous thighs, and expressed disgust for fat people. She would have liked to see him more active and called him a "sissy" and a "mamma's baby," but was unable to develop a better social adjustment in him.

*Course.*—After the first visit to the Obesity Clinic, the patient did not return and follow-up letters remained unanswered. This was astonishing in view of the former excellent cooperation. The explanation was

given one year later (May, 1940) when the mother brought the child back to the clinic for further treatment. She herself had been seriously sick and had been in the hospital and a convalescent home for about six months for operation of a tuberculous kidney. She was still under medical care for an infection of the wound. The father had become suddenly ill with an "acute nervous collapse" and had been unable to work for several months. The household had to be dissolved, and during this year the patient had been shifted from place to place. None of the relatives kept him over a long period of time. Finally, an older woman of the neighborhood took him to board with her. She was crippled and was unable to give him much supervision and assistance.

Considerable change had occurred in the patient who was now 7 years old. He had grown 2 in. and had lost 5 pounds, but continued to be overweight (29 per cent). There was a striking increase in the size of the genitals, more so than is generally observed in boys between 6 and 7 years. However, no other signs suggestive of precocious puberty were present, although this possibility must be kept in mind.

The boy had been left, to a large extent, on his own responsibility and had gained in personal security. He had learned to take care of himself and dressed and bathed unaided. He no longer suffered from fear when left alone, but often preferred to remain at home rather than accompany his mother. Should she not be at home when he returned from school, he played on the street and did not hesitate to join other children, although his play was still less active and rough than that of other boys of his age. He had also become more aggressive and more efficient in defending himself during the past year. A psychometric examination revealed that the patient was of average intelligence as measured by the Stanford-Binet test, but less proficient if measured by the performance tests of the Arthur point scale. The response to the Rorschach ink blots revealed anxiety trends which interfered with his intellectual functioning and severe emotional concern over his health and physical development.

*Summary.*—The case has been presented of a 6-year-old boy in whom obesity had developed during long-continued treatment with gonadotropic substance for an undescended testicle. The patient had shown mild manifestations of allergy during infancy. He reacted to the injections with severe general symptoms such as irritability, sleepiness, and nausea. The treatment and his reactions to it stimulated overprotective measures and overfeeding by the mother and provoked anxiety symptoms in the patient. The immediate mechanism of the obesity in this patient can be explained on the basis of overfeeding and inactivity. The concurrence of glandular treatment and development of obesity is not only a chronologic coincidence, but also a revelation of a causal interrelationship.

CASE 2

*Medical History.*—The patient, E. G., came to the Pediatric Department of Vanderbilt Clinic for the first time on Sept. 7, 1933, at the age of 5 years and 2 months. The chief complaint was attacks of asthma for the last six months. The girl had been subject to frequent sneezing since birth. Several members of the maternal family were said to suffer from frequent sneezing. There had been no eczema or other allergic manifestations. Tonsillectomy was performed at 2 years of age, without influencing her tendency toward sneezing or repeated colds. The first asthmatic attack had developed following mumps at the age of 4½ years. There had been five severe attacks of several days' duration. Physical examination showed no significant finding. The Mantoux test was negative. A roentgenogram of the chest showed a striking increase in the lung markings, but gave no evidence of parenchymal involvement or of tuberculosis. The findings were considered consistent with changes in frequent colds and asthma.

The child was referred to the Allergy Clinic for study and treatment. She remained under the care of that department for one year, and there was marked improvement under a regime of elimination diets and ephedrine medication. The last asthmatic attack was recorded on April 17, 1934. In September, 1934, she was discharged from the Allergy Clinic, having been free from all symptoms during the summer. She was advised to return in case symptoms reappeared, but no further visits to the Allergy Clinic were made. At each of the later visits to other clinics, information concerning the asthma was obtained. No more attacks were reported. There was one visit to the Oto-Laryngological Clinic in February, 1936, for nosebleeds and sniffling. The findings were so insignificant that no return appointment was given. In recent years the girl suffered from occasional colds and nasopharyngitis with sneezing, but no asthma.

*Thyroid Enlargement and Therapy.*—On Sept. 7, 1934, when the patient was 6 years and 2 months old, a moderate enlargement of the thyroid was noticed at a general checkup. The child was sent to the Thyroid Clinic where she was followed regularly during the next five years.* The thyroid was described as nodular, especially the right lobe, and rather firm. Manifestations of hypothyroidism were searched for carefully, but none were found at any time. The possibility that the asthmatic attacks might be associated with a substernal extension of the thyroid was discussed but excluded by roentgenographic examination. Skeletal maturation was found to be normal. Her physical and mental development had always been normal. The determination of the basal metabolism gave a rate of –30 per cent (surface area standard). In

*I am indebted to Dr. L. W. Sloan for permission to make use of his observations of the patient.

view of lack of signs and symptoms of hypothyroidism, an experimental error was suspected and the basal metabolism determination was repeated one week later. To insure an accurate result, the patient was admitted to the Babies Hospital for the test. The result was a rate of –13 per cent on surface area standards. Calculation of the rate on basis of height or weight standards (Talbot) gave values of +5 per cent (height) and –1.6 per cent (weight), respectively. The finding was interpreted as indicating normal thyroid activity. For prophylactic purposes, courses of thyroid and iodine medication were advised and were given for the next two years. The total amounts given were small: whole desiccated thyroid* in doses of 0.03 Gm. three times daily for two weeks three times a year, and 2 drops of hydriodic acid syrup for the same periods.

She was re-examined every three months during the next two years, and every six months later on. At each visit a careful examination for possible hypothyroid symptoms was made, but none were present at any time. There was no further enlargement of the gland, and in May, 1937, when the patient was 8 years and 11 months old, it was felt that the gland was becoming smaller and was no longer nodular. In 1939 the gland was no longer considered enlarged, and the slight bulging of the neck could be explained as accumulation of fat. A basal metabolism determination in June, 1938, gave an essentially normal value. The rate was ±0 according to Talbot's height standards, –8 per cent on weight standards, and –19 per cent on surface area standard. Serum cholesterol was 229 mg. per 100 c.c. serum.

*Physical Growth and Weight Development.*—The weight at birth was 8½ pounds. Throughout infancy and early childhood her progress was satisfactory, and she was always considered a big child. There was no delay in the eruption of teeth or the onset of walking and talking. At 5 years and 2 months, at the time of the first visit to the clinic, the girl was 45½ in. tall and weighed 48 pounds; that is, she was somewhat taller and heavier than the average child of her age, but not overweight (Fig. 4). During the following year, while under treatment for asthma and receiving different elimination diets, her weight increase was but slight. She weighed 50 pounds in September, 1934, when the thyroid enlargement was first noted. From that time on, there was a rapid gain in weight and she weighed 75 pounds in October, 1935, an increase of 25 pounds in thirteen months. During the following years the rate of gain was not so steep, but was greater than that of a normal girl. In May, 1936, she was markedly overweight. Her condition was explained on the basis of overfeeding, although the possibility of an endocrine factor was also discussed, but was rejected in the absence of other signs of glandular disturbance.

*Burroughs Wellcome & Co.

In October, 1939, at the age of 10 years and 5 months, she was referred to the Pediatric Obesity Clinic. She presented the picture of an oversized and markedly overweight girl. Her height was 59½ in. and her weight was 126 pounds, 36 pounds, or 40 per cent, overweight.[1] Secondary sex characters were well developed, but menarche had not yet occurred. Otherwise, the physical examination failed to show abnormalities. The thyroid gland could not be felt; the neck looked rather full because of the accumulation of fat. The food intake was described as very high, and the obesity could well be explained on a dietary basis.

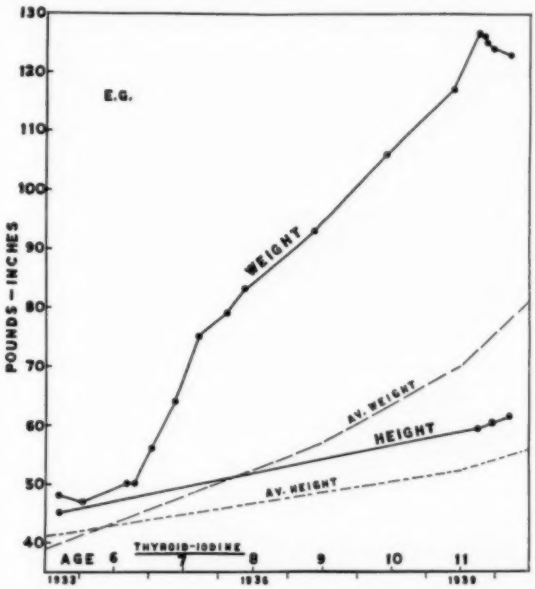


Fig. 4.—Height and weight development of E. G. (Case 2). Age is given in years. The heavy lines represent the height and weight of the patient; the interrupted lines, the average development.

*Behavior Aspect.*—The mental development of the girl offered no obvious abnormality. Her progress in school was adequate. The mother stated that the girl had never been as active as the average child, that she just sat about and would not move. On further questioning it was found that this inactive behavior had been fostered by the parents and that the girl had started to rebel against the overprotection. Association with other children had always been restricted, and she had never been allowed to go out in cold weather or on rainy or snowy days. In winter the mother would take her to protected spots and stand quietly in the sunshine, not allowing her to play in the snow with other children. Little freedom had been given to the girl in her personal

care; she was not allowed to take a bath alone (not even later at 12 years of age) and was still being sent to the toilet. The child had always been a good eater, but had vomited at the slightest provocation when younger. In recent years her demand for food between meals, especially for candy, had increased more and more.

*Attitude of Parents Toward Patient and Her Health.*—The patient was an only child. The mother said that she would have liked to have had another child, but her husband felt they had better have only one child and give her a "rich life" rather than divide the little they had with more children. The major concern of the parents centered around the asthmatic attacks. From the dramatic description which the mother gave, one would think that the child had suffered from severe attacks continuously up to the present and not that the last attack had been at the age of 6. The parents still lived in constant fear of asthma and were afraid to relax the precautions which had been devised to protect the child from exposure to cold and infection.

The obesity was explained by the patient and her parents as being due to her "lazy gland," although the family had been reassured repeatedly that the function of the thyroid was normal. Of the numerous laboratory examinations, the mother remembered only the first basal metabolism determination which had been reported erroneously as –30 per cent. This low figure was the family's explanation for the child's obesity and inactivity. The mother did not remember that there had been a marked increase in weight when the child was 6 years old. When confronted with the figures of the clinical record, she was inclined to blame the record for errors.

When dietary changes were discussed, the mother expressed fear that it might be harmful for a child with a "lazy gland" to lose weight and was unwilling to accept advice. The patient was openly antagonistic to any treatment.

*Course.*—Cooperation in this case was poor and appointments were broken frequently. Both the patient and her mother were convinced that the "glandular condition" would prevent any weight reduction. In addition, the patient claimed that she became carsick and therefore could not come to the clinic, adding that she became carsick only when travelling with her mother. The patient objected to dietary restriction, and her mother was unwilling to relinquish the protective and restricting measures. There was no further gain in weight, even a slight loss, during the next six months. However, the prognosis for a real change in the patient's condition and a different attitude toward it is poor.

*Summary.*—The case has been presented of a 10½-year-old girl in whom obesity developed after the age of 6 years. A marked increase in weight occurred after an enlargement of the thyroid had been noted and the possibility of endocrine disorder had been suspected. Although

continued clinical observation excluded symptoms of hypothyroidism, the family was unable to accept later reassurance on this point. The concept of a "lazy gland" had become deeply ingrained in the patient's and her parents' minds. The obesity had resulted from marked overfeeding and restriction of physical activities. These precautions and overprotective measures had been provoked by the constant and exaggerated fear that asthmatic attacks, which had cleared long ago, might recur.

## DISCUSSION

1. *Thyroid and Pituitary Preparations in the Treatment of Obesity.*—The concept that obesity is the result of an endocrine disturbance and that glandular medication is necessary for its treatment has been so extensively propagated that authors who found they were able to cure obesity without hormonal products state this fact in the title of their reports.[2] A study of the literature of the last decade reveals an increasing number of articles which plead for a more critical attitude toward the extravagant claims of endocrine successes. An evaluation, however, of the treatment that had been suggested or carried out in a large group of obese children before they were referred to the clinic indicates that administration of endocrine products constitutes, for the majority of practicing physicians, the treatment of choice and often the only therapy in obesity of childhood.

Endocrine treatment of obesity refers in most cases to products of the thyroid and pituitary glands, although preparations of practically all endocrine glands have been described as helpful, without their becoming so popular. Oral administration of thyroid gland deserves the merit of priority. It was introduced into therapy in 1894 by Yorke-Davies[3] in London and Leichtenstern and Wendelstadt[4] in Cologne. These early reports emphasize the need for simultaneous dietary restriction and reserve thyroid medication for exceptional cases, especially for anemic and chlorotic patients. The reported successes stimulated enthusiastic expectations for an effortless treatment of obesity. Only six years later, in a well-known monograph on obesity, von Noorden[5] expressed his disappointment over the failure of thyroid therapy, saying that "today [in 1900] one would turn one's back on it." This skeptical evaluation with which von Noorden reviews his lack of success with thyroid is the more remarkable because the concept of a slow and retarded metabolism as the cause of obesity, in the so-called endogenous type, was formulated by him; the finding of a "low metabolism" later became synonymous with the diagnosis of hypothyroid obesity. Despite this critical attitude of von Noorden, thyroid has remained the most widely used medication for obesity.

Usage of thyroid is being defended on two grounds, as specific replacement therapy or as a calorigenic drug. The concept that obesity is

the result of thyroid underactivity is no longer tenable in view of the convincing evidence that no metabolic disturbance exists which would justify this diagnosis (Newburgh and Johnston[6] and numerous other reports). The opinion prevails, however, that obesity in childhood is per se an indication of endocrine disturbance. As late as 1937, Gordon[7] stated that the underlying cause of obesity in childhood was mainly endocrine. Recent investigations of this department[8] and of Talbot and Worcester[9] showed that, in contrast to hypothyroidism, the rate of growth and maturation of obese children is accelerated. Furthermore, as in obese adults,[10] the basal metabolism of obese children is higher than that of normal children, another finding that stands in direct contrast to hypofunction of the thyroid gland.

The use of thyroid, not as biologic substitution, but as drug therapy for its calorigenic action implies the production of hyperthyroidism. Means[11] expresses himself as opposed to its use for such a purpose. In contrast to the definite, precise, and predictable effect of thyroid in hypothyroidism, he describes its action in nonthyroid conditions as unpredictable and disappointing. In order to obtain a stimulating effect on the metabolism, much larger doses are needed than are generally given to obese patients. The claims of the specific value of thyroid in the treatment of an obese child can be discarded frequently on the basis of insufficient dosage alone.

That a relationship exists between obesity and pituitary function was first postulated by Fröhlich in 1901.[12a] He recognized that the occurrence of obesity and sexual underdevelopment in patients suffering from tumors at the base of the brain represented, not an accidental coincidence, but a possible relation to the tumor. His assumption that the presence of such trophic disturbances pointed to the hypophysis and indicated interference with its endocrine function has not been borne out by subsequent clinical or experimental evidence.[12b] Fröhlich himself considers his original pituitary interpretation as no longer correct.[12c] His original assumption, however, has remained exceedingly popular, and the diagnosis of pituitary disturbance constantly is being made in obese children who show a distribution of fat tissue similar to that of Fröhlich's patient and in whom puberty has not yet made its appearance. It must be pointed out that the description of the original case in no way claims that the localization of the accumulated fat was specific for lesions of the pituitary gland. Fröhlich speaks of the fat accumulation in the broad term "trophic disturbance."

Diagnosis of a pituitary hypofunction calls, of course, for replacement therapy. Numerous extracts of the pituitary gland have been prepared and extravagant claims about their specific value have been made. Unlike thyroid substance, pituitary extracts have been found to be ineffective when given by mouth, even if the preparation is not entirely void of active substance.[13] Despite this fact, reports continue

to be published with the intention of showing the striking and specific effect of oral administration of pituitary extract. As an example, a paper by Lurie[14] will be discussed. His paper contains more information on the patients than is generally recorded in papers of this type. Lurie reports the cases of two boys, 15 and 14 years of age, who were markedly obese and whose genitals were "functionally immature." On the accompanying photographs the genitals appear to be in the beginning of puberal development, and the "female type" of distribution of the pubic hair corresponds to the early stage of pubescence. Both patients were admitted to a child guidance home and received some pituitary extract by mouth for many months. Both lost weight, and their genital development showed marked progress six and twelve months later. Lurie considers the loss in weight and progress in genital maturation as evidence of the specific efficacy of pituitary extract by mouth. He denies the possible effect of any other influence, specifically denying that the loss in weight could be explained on a caloric basis because no detailed dietary prescription was given. The first case history reports that the patient's diet was restricted only with regard to candy and pastries and that the patient cooperated well. Concerning the second patient, the report states: "In the beginning he broke his promise and satisfied his inordinate craving for carbohydrates." Loss in weight of this patient was intermittent at first. "This was due to the fact that the boy did not always take his medicine regularly. . . . Gain in weight or failure to lose weight could always be attributed to failure to take his medicine." The report contains no evidence as to the validity of the conclusions and no reason on the basis of which it could be excluded that poor cooperation with the diet was not responsible for the failure to lose weight; nor does it explain why limitation with regard to candy, ice cream, and pastry does not represent a dietary restriction worthy of accounting for the loss in weight, particularly in patients who before treatment ate "tremendous" amounts of carbohydrates. No consideration is given to other possibilities, such as social factors or adjustment in interpersonal attitude and relationship, factors which suggest themselves immediately because both patients were removed from their former environment (about which nothing is being said) and were placed in a child guidance home.

This paper is an example of the fallacy of attempting to draw conclusions about the specific value of a certain medicine from the therapeutic result, without taking into account the complexity of the manifold factors involved in treatment. The paper seems to be of value in so far as it demonstrates that the cooperation of the patient is more important for weight reduction than a carefully calculated and severely restricted diet which will be broken over and over again. Any kind of "medicine" may be of suggestive value and thus helpful

in sustaining cooperation over a long period of time; but this fact is certainly not a proof of a "specific" value of the oral administration of pituitary gland.

In recent years pituitary preparations to be given as injections have become available. A number of them contain active principles, mainly the growth-promoting, gonadotropic and thyrotropic factor. The gonadotropic preparations which are widely used in the treatment of obese children and adolescents are obtained from the anterior pituitary lobe or pregnancy urine. The reports are not always clear as to whether the preparations are applied for correction of some genital deficiency or for weight excess. Authors[15] who recommend glandular treatment of obesity seldom fail to restrict the dietary intake simultaneously. The results which are obtained by dietary restriction alone, without any glandular treatment, are as striking as those which are attributed to the specific effect of the endocrines.[16] The cooperation of the patient is essential for a good result, and it seems that the frequent office visits which glandular therapy entails play an important part in enforcing cooperation in otherwise refractory patients. Gonadotropic substance alone, without dietary restriction, leaves the obesity entirely unaffected.[17] That the frequent injections may even provoke development of obesity was illustrated by the first case presented in this paper.

Contrary to the experience with true glandular disorders, it is claimed that the endocrine condition in obesity will be influenced by a variety of glandular products. Results reported by one author cannot be duplicated by others, or equally good successes can be obtained without any endocrine therapy. Furthermore, when glandular extracts seem to be effective, the results are frequently permanent and no further "replacement" therapy is required. In true glandular deficiency, interruption of treatment is followed by recurrence of symptoms. This occurs so regularly that it may be used as a diagnostic test in childhood hypothyroidism where improvement may be so marked that the original diagnosis is open to question.[18] The specific effect of thyroid administration and withdrawal on the blood serum cholesterol in hypothyroidism and the complete absence of this effect in obese children have been reported previously.[8b] The observation that obesity develops as the result of simple overfeeding and can be cured by dietary restriction alone seems to be sufficient evidence to dispose of any necessity to invoke an endocrine mechanism. This conclusion is supported further by the absence of any specific effect of thyroid and pituitary products in the treatment of obesity.

2. *Obesity in Childhood and Cryptorchidism.*—Cryptorchidism and endocrine obesity are so frequently diagnosed in the same child that a discussion of their relationship seems to be indicated. Bigler, Hardy,

and Scott[19] review the results of treatment reported by eighteen authors and give some figures which are of interest in the problem. The diagnosis of undescended testicle is being made about ten times as often in children as in adults. The United States Army reports an incidence of 3.1 for each 1,000 recruits. In a survey of the New York Hospital for the Ruptured and Crippled, incomplete descensus was recorded in 3 per cent of 18,140 children. These figures suggest that, in about 90 per cent of the children in whom the diagnosis is being made, the testicles will descend spontaneously. Of the 191 patients included in the review of Bigler and his co-workers, 101 (52.8 per cent) were described as possessing an "endocrine type of obesity." This figure indicates that obese children furnish a large contingent of the so-called cryptorchid patients in whom spontaneous descent will occur later. How greatly the viewpoint of the observer influences the diagnosis of cryptorchidism in obese children will be illustrated by figures given by different authors. Gordon[7] found signs of hypogonadism in twenty-seven of the twenty-nine boys of his series and considered this finding indication for hormonal treatment. Of the twenty-seven patients, fifteen showed descent of testes, seven bilateral cryptorchidism, and five unilateral cryptorchidism. In a previous report on the group under study in this department,[8a] only one patient among fifty-one boys was recorded as showing undescended testicles which had been treated, without success, with gonadotropic substance. On another patient orchidopexy had been performed before he came under observation for obesity. Among the remaining forty-nine boys, ten showed incomplete descensus, which means that the testicles were found at repeated examination in different positions in the scrotum or near the inguinal region, a condition which was explained as the result of nervous excitability and high activity of the cremasteric reflex and which did not warrant hormonal treatment.

Such wide divergence in diagnosis is an expression of the uncertainty that exists at present as to what constitutes an "imperfect descent of the testis." Several British authors, basing the reports in part upon observations of boys followed for many years in the British public schools,[20] took issue with this problem. Browne[21] calls attention to a series of misconceptions which lead to incorrect diagnosis and subsequent treatment which is not indicated by the actual condition. He mentions the failure to recognize the normal variations in the position of the developing testis, and he considers as normal in childhood any position from which the testis will invariably reach the scrotum. A common misconcept is the idea that a testicle which can be felt in the region of the inguinal canal is actually in that canal. A migratory testis, which frequently accounts for the diagnosis of an "undescended" testicle, is never withdrawn into the inguinal canal by the cremaster. As to treatment with gonadotropic substance, he expresses the opinion that it will

not bring down any testis that would not have descended without it, although it will hurry the descent. True ectopic position requires operative correction. Spence and Scowen[22] report also that only the movable retractile testis will respond to hormonal treatment and will do so within three months. Failure to respond to hormonal treatment suggests an anatomic abnormality. Bigler, Hardy, and Scott[17a] found that, if a testicle is going to descend, it will do so before 4,000 R.U. have been given. In none of the treated children in their series was there any change in the type of body build, either during the course of treatment or during the later period of observation.

The uniformity of opinion in the reports of the last two years is in good agreement with the original experimental work that stimulated the widespread, and at first often indiscriminate, usage of gonadotropic substance for the treatment of undescended testicles. Engle,[23] in 1932, showed that it was possible to induce experimentally the descent of testis in young *Macacus* monkeys by hormones from the anterior pituitary and pregnancy urine. The testicular descent occurs normally with the first phases of puberty. The administration of the hormone merely serves to accelerate a process which will occur spontaneously.

In obese boys the uncertainty as to the state of descent of the testicles is aggravated by the circumstance that excessive accumulation of fat in the pubic region often conceals the true size of the genitals and renders examination more difficult. The concept that obesity is an expression of some endocrine disturbance further obscures the issue. The argument for the diagnosis of a glandular disorder is used in both directions. The presence of obesity in an alleged case of undescended testicles, or, vice versa, the incomplete descensus of the gonads in an obese boy, support each other as evidence of the endocrine nature of the condition. Both findings seem to warrant endocrine therapy and thus expose boys to long-continued treatment for which, to say the least, no factual indication exists.

There remains one useful application of the gonadotropic substances in obese children. In a few instances the problem of whether spontaneous descent will occur remains questionable even after repeated examination. Gonadotropic preparations are of value in these rare cases in identifying those testes which are truly ectopic and cannot descend spontaneously and which should be operated upon at an early age.

3. *The Dangers of Endocrine Therapy in Childhood.*—Authors who continue to advocate the use of endocrine products in obesity in childhood are not unaware of all the negative evidence which has been accumulated against the specific value of these products. In favor of active glandular therapy the argument is used that the risk of failure

to develop normally is too great to allow a patient to remain untreated, the more so as the treatment involves no danger of untoward effects. This assumption that glandular therapy is entirely harmless is as incorrect as the possibility of maldevelopment is exaggerated. Although reports about undesirable effects of gonadotropic substance are not numerous, the occurrence of precocious sexual development[24] and of glycosuria[25] has been described. Severe general reactions to the injections, as in Case 1, are not uncommon. They are mentioned with such frequency by patients who had received injections before they came to the attention of the clinic, that it may be assumed that reports of untoward effects of this type do not usually find their way into the medical literature. Since gonadotropic substances have been in use for only a few years, nothing can be said at present about undesirable consequences in later life. The possibility that the overstimulation of the immature gonads may result in functional impairment cannot be discarded. The editorial warning of the A. M. A.[26] against "undiscriminating injection of unknown substances into unsuspecting patients" is still justified. The careful therapeutist will refrain from administering these preparations without strict medical indication.

More serious, however, than the possibility of harmful physical effects appears at present the danger of psychologic injury through the indiscriminate diagnosis of endocrine disorder and the subsequent glandular therapy in obese children. This statement is made in opposition to claims of beneficial effect of glandular therapy on the mental and emotional development of obese children. Their peculiarities of reaction, the lack of aggressiveness, and the slow and submissive behavior have been attributed to hormonal deficiency,[27] and these characteristics are therefore considered another indication for glandular therapy. Other authors[28] call attention to the "untold and often irreparable psychic damage" which may result from inferiority feelings in reaction to the physical deficiency and ungainly appearance. The only way of saving the patients from this fate and of preventing disaster has been asserted to be extensive glandular therapy. Such gloomy predictions and such sweeping claims of miraculous mental and emotional transformations as the result of glandular therapy, "almost immediately after the start of the injections" are usually presented in general terms only, without adequate case studies and without critical and controlled evaluation of the multiform happenings.

The emotional problems were studied in their various aspects by Mittelmann[29] and Davidoff.[30] They both failed to observe an automatic transformation of behavior through hormonal therapy or to find a definite correlation between mental improvement and correction of the endocrine status. The total behavior, the poverty of drive, the sluggishness and overdependence could not be explained as resulting from glandular deficiency or as psychologic response to the physical condition,

but rather suggested the importance of additional factors. Feelings of inferiority were found infrequently in patients with cryptorchidism. Many patients had been unaware of the condition, as were their parents or physicians. Disturbing psychologic symptoms developed only after attention had been called to the condition.

My own observations are in agreement with the findings of these authors. Investigation of the etiology of the excessive food intake[16] and avoidance of muscular activity[31] points to an emotional significance of these symptoms. While inherent constitutional factors play a definite role in the development of obesity, important contributory features were revealed through a study of the environmental forces.[32] It was found that most obese children are exposed to excessive overprotection and oversolicitude; however, the overt manifestation of these attitudes barely covers the underlying hostility and rejection by the mother. In such an environment, which does not offer adequate emotional security, food gains an inordinate importance and stands for satisfaction, security, and love. The atmosphere of fearful apprehension confers upon social contacts and muscular activities the meaning of danger, threat, and insecurity. The development, in such surroundings, of obesity and of immature and overdependent behavior becomes comprehensible.

In a family with this attitude of overanxious concern, the diagnosis of an endocrine disorder in the child is not an indifferent happening. It serves to aggravate the attitude of general overprotectiveness and to increase and justify the excessive care and overfeeding of the child. At the same time, it seems to promise a simple, effortless treatment through pills and injections which will transform all undesirable traits of the child. Once the family has been convinced of the "bad glands" of the patient, the road to a more rational approach of treatment is blocked, as is illustrated by the second case of this paper.

If the endocrine diagnosis implies a poor prognosis for sexual development or indicates its existence, underlying emotional conflicts may become activated. In many cases both the patients and their parents were seriously disturbed after having been frightened by this diagnosis. In none of my patients who had been rendered miserable and unhappy by this information was the diagnosis of sexual maldevelopment justified. A pertinent case history with marked anxiety, changes in behavior, and rapid increase in weight after the spectre of sexual abnormality had been held before the patient, has been reported in a previous paper.[16] A series of other case studies has been included in the study of the family constellation.[32] Objective reassurance is of little avail in many cases. Some mothers may plead for active glandular therapy or take the patient to another physician. Their problems, however, are not solved by injections which, in many cases, only serve to confirm the fear that something fundamental is irreparably wrong with the child.

The two cases presented in this paper serve as illustrations of how prolonged glandular therapy and the suspicion of a glandular disorder may have a harmful influence on the whole life of the child and thus may even produce obesity. There is no reason to assume that the hormones had a paradoxic physiologic effect in these patients; the amounts given in the second case were quite small. The development of obesity in both patients can be explained if the effect of the diagnosis and treatment on the patient as a child in a solicitous family circle is taken into account. In the first case, the injections acted directly as a sick-making agent. The overdependence of the child and the overanxious concern of the parents were provoked through this repeated disabling event. Since the child was quite young and the treatment was carried out over a long period, the whole behavior of the child and the attitude of the family were determined by these experiences. The resulting picture closely resembles that observed in other obese children in whom entirely different circumstances led to a similar passive behavior and overprotective measures. The accustomed pattern persisted even after the injections were discontinued. A number of serious changes in the environment, however, which occurred during the last year of observation, brought about a marked change in the behavior of the child, bringing out those qualities which had been thwarted under the influence of continued invalidism. The attitude of the parents who wanted everything done to avert maldevelopment of their child, even though it implied considerable discomfort, appears to be natural and understandable. Later on there was much effort and good cooperation to counteract the undesirable consequences.

In the second case the primary attitude of the family disclosed an unusual degree of solicitude and apprehension which had always made each physical symptom of the child an upsetting event. The constant fear of recurrence of asthmatic attacks led to a series of precautions which resulted in overfeeding and restriction of activity. The attitude of this family may be considered typical of that observed in families of most obese children.[32] The possibility of glandular disorder which the thyroid enlargement seemed to indicate only served to aggravate the excessive care and overprotective measures. At the same time, it afforded a convenient excuse for the developing obesity which, in turn, further confirmed the assumption that the glands were wrong. This aggravating influence of the diagnosis of an endocrine disorder in an obese child is quite common and makes this diagnosis a serious obstacle for a recognition of the underlying problems and successful treatment.

## SUMMARY AND CONCLUSIONS

The case is reported of a 6-year-old boy in whom marked obesity developed while receiving gonadotropic substance. Another case is reported of an 11-year-old girl who grew obese after a thyroid enlarge-

ment had been noted. It could be demonstrated in both instances that the obesity stood in causal connection to the diagnosis and treatment, respectively. They stimulated or aggravated an overanxious and protective attitude of the families which led to overfeeding and restriction of activity and thus to obesity.

The diagnosis of an endocrine disorder in an obese child and long-continued glandular treatment are not only unjustified, but harmful, in so far as they produce or increase the apprehensive and oversolicitous attitude of the parents and block the road for a rational treatment of the obesity.

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# CREATINE AND CREATININE METABOLISM IN HYPOTHYROIDISM

## With Special Reference to the Limitations of Using Creatinine in the Urine as a Standard of Basal Energy Metabolism

Ch'uan Fan, M.D.
Peking, China

IN HIS paper, "Laws Governing the Chemical Composition of Urine," Folin[1] pointed out the fact that the daily urinary output of creatinine is remarkably constant in normal adults despite the variations in diet. The constant daily amount was later found to be proportional to the body weight, and was not affected in conditions which might influence the amount of creatine in the urine. These remarkable facts led to the conclusion that creatinine is a product of endogenous metabolism, excreted in proportion to the amount of active protoplasmic mass in the body.

Creatine is absent in the urine of normal adults, even though it is present in the muscles in appreciable amounts. In view of the close chemical relationship between creatinine and creatine, the origin of creatinine from creatine was at first taken for granted. It was later observed, however, that the ingestion of creatine by normal adults resulted in either complete or partial retention of the substance by the body, without its being excreted as creatinine. On the other hand, ingested creatinine was promptly excreted. Much doubt arose as to whether the organism was able to convert creatine into creatinine. This question was not settled until 1923 when Benedict and Osterberg[2] demonstrated conclusively the conversion of creatine into creatinine. While the urinary creatinine showed no immediate change after the feeding of creatine to animals, it started to increase definitely after the second week of creatine ingestion, thus showing that a large part of the ingested creatine was converted in the organism into creatinine. On discontinuance of the creatine administration, the creatinuria immediately stopped, but the increased level of creatinine excretion was maintained for at least seven weeks. The conversion of creatine into creatinine is, therefore, one of the slowest metabolic processes known to occur in the animal organism.

While creatinuria is absent in normal male adults, it is found to occur in women and children and in certain pathologic states, chiefly those affecting the muscular and the endocrine systems. For instance, creatinuria is diminished in children with hypothyroidism, but it increases on thyroid therapy. On the basis that this increase in creatinuria

From the Division of Pediatrics, Department of Medicine, Peiping Union Medical College.

occurs earlier than the changes in either the basal metabolic rate or the blood cholesterol level, Poncher, Visscher, and Woodward[3] suggested in 1934 that the change in the creatinuria might serve as a clinical guide in the substitution therapy of hypothyroidism. In 1935, Bodansky[4] found that the feeding of thyroid causes a lowering of the creatine content of tissues and muscle in association with the creatinuria. If the amount of creatinine excretion depends on the amount of available creatine in the body, as was demonstrated by Benedict and Osterberg,[2] it follows that, with the depletion of creatine in hyperthyroidism, the creatinuria ought to diminish. Yet, it is generally held that creatinine excretion is not influenced by the level of thyroid activity.[5]

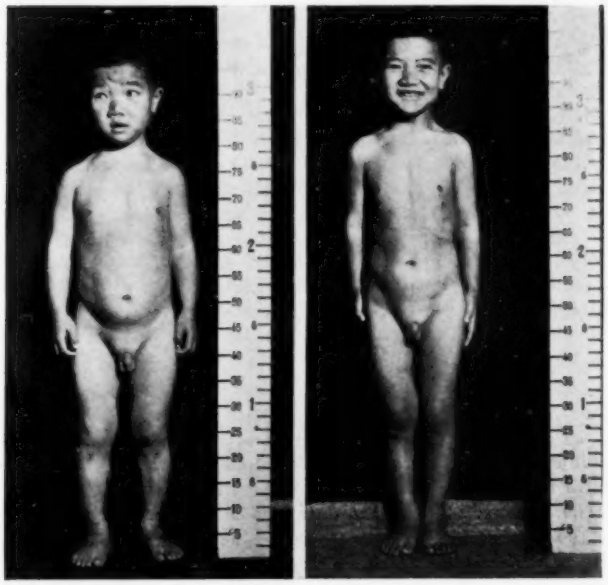
This apparent paradox is not only of theoretical interest but also of clinical importance, because urinary creatinine has been proposed repeatedly to serve as a standard of basal metabolic rate. It has been questioned that body surface per se should be the determining factor in the production of heat in the animal organism. It was frequently inferred that the basal metabolic rate could be expressed in terms of body surface, body weight, or age, simply because these factors are all proportional to the amount of active protoplasmic mass in the body. While this relationship may be normally constant and predictable, it may be grossly disturbed in cases where the body proportions are abnormal, such as in obesity. It may be more desirable, therefore, to express the basal metabolic rate in terms of excretion of creatinine which is supposed to be an endogenous metabolic product excreted at a constant rate per unit of active body tissue. Indeed, as early as 1914, Palmer, Means, and Gamble[6] had made such a proposal. More recently, Talbot[7] has applied the principle to the determination of basal metabolic rates in children. The practical application of such a standard, naturally, presumes a constant proportionality between the level of creatinine excretion and the amount of active body tissue, despite circumstances which might affect the basal metabolic rate. Therefore, the degree of constancy of creatinine excretion at varying functional levels of the thyroid gland assumes a new practical importance.

In 1935, we had three cases of hypothyroidism on our wards. The occasion was utilized, therefore, to study further the changes in creatine and creatinine excretion, before and after thyroid therapy.

## EXPERIMENTAL SUBJECTS

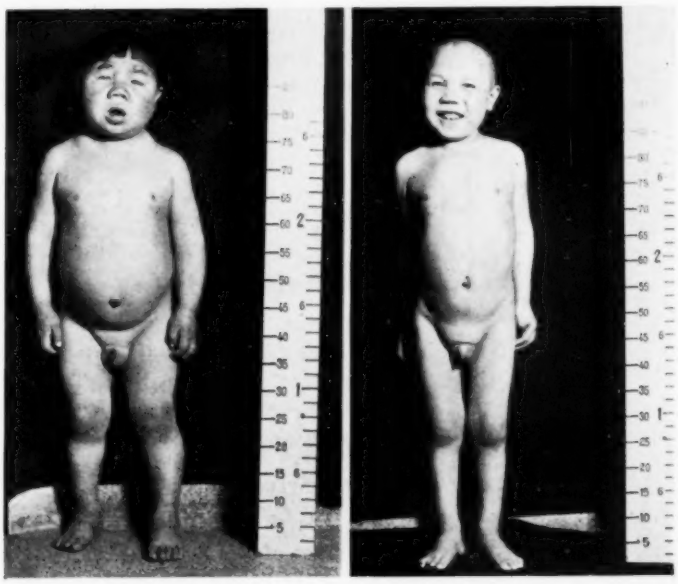
C. Y. S. (51945), a Chinese boy 12½ years of age, was noticed to be physically retarded since birth. He was unable to talk clearly until 3 years of age, and was never able to walk steadily. His height was 104 cm., and weight, 17.9 kg. His general appearance was that of a 5-year-old boy. His skin was rough and his hair coarse. He was mentally dull and physically sluggish. His basal metabolic rate was -14.5 per cent. Bony age by roentgenologic examination was between 4 and 5 years. (Fig. 1.)

W. S. T. (48720), a Chinese boy 13 years of age, had a history of retardation in physical and mental development noticed since 1 to 2 years of age. He did not



*A.* *B.*

Fig. 1.—C. Y. S. *A*, Nov. 26, 1935, before treatment; *B*, Oct. 9, 1936, after thyroid treatment.



*A.* *B.*

Fig. 2.—W. S. T. *A*, March 9, 1935, before treatment; *B*, Aug. 29, 1935, after four months of thyroid treatment.

learn to talk until he was 5. His height was 98.6 cm., and weight, 23.5 kg. His general appearance was typical for that of a cretin. His mental age was estimated to be 3½ years, and his bony age, 4 years. His basal metabolic rate was -24.5 per cent. (Fig. 2.)

T. A. N. (33817), a Chinese girl of 7 years, was first seen in 1931 for mental and physical underdevelopment. Her height was 87.5 cm., and weight, 10.6 kg. Her general appearance corresponded to that of a child of 3 to 4 years. The mental age was estimated to be about 8 months. Her basal metabolic rate was not determined because of the technical difficulties. The bony age was slightly below her chronologic age. After thyroid therapy, her mental and physical condition improved quite rapidly. She took the dried gland intermittently. By May, 1933, her basal metabolic rate had reached +19 per cent. Thyroid medication was then discontinued. In January, 1935, her basal metabolic rate was about -5 per cent. Her height was 109 cm., and weight, 19 kg. Her mental age was estimated to be around 3½ years.

## EXPERIMENTAL

After varying periods of study on the pediatric ward, the subjects were transferred to the metabolic ward where quantitative preparation of diets and complete collection of excreta were carried out under strict supervision. During the period of study, the subjects were allowed to walk about in the ward. At the end of each day, they were instructed to empty their bladders as completely as possible.

The urine specimens were kept on ice as soon as they were voided, with toluol or chloroform as preservative. Analyses were made each day by Folin's method.[8] Creatine was dehydrated by autoclaving with picric acid purified by crystallization as sodium picrate.[9]

The diets (Table I) were kept constant during the entire periods of study. T. A. N. had meat throughout the period of study, but the other two subjects were on meat-free diets during the periods of metabolic studies.

TABLE I

DIETS OF THE EXPERIMENTAL SUBJECTS

| SUBJECT | CALORIES | PROTEIN | MEAT | MILK | EGG |
|---|---|---|---|---|---|
| C. Y. S. | 1200 | 45 | — | 450 | 3 |
| W. S. T. | | | | | |
| (April, 1935-June, 1935) | 1200 | 45 | — | — | 3 |
| (Dec., 1935-May, 1936) | 1200 | 45 | — | 450 | 3 |
| T. A. N. | 1200 | 40 | 50 | — | 2 |

## RESULTS AND DISCUSSION

The results of the study are shown in Figs. 3, 4, and 5. The daily urinary excretion of creatine showed marked fluctuations which were not eliminated with the omission of meat from the diet. To simplify the charts, the mean values of every three or four days were used. Even then, the values were by no means constant.

### BLOOD CHOLESTEROL

The change in the blood cholesterol level during the course of thyroid administration was studied in the cases of W. S. T. and C. Y. S. In Figs. 3 and 4, it is clearly shown that the level had roughly a reciprocal relationship with the basal metabolic rate. But, in addition to the general trend, there were less prominent fluctuations which bore no rela-

tionship to energy metabolism. Apparently the blood cholesterol level was also influenced by factors which did not affect the energy metabolism. Therefore, it did not serve as a useful guide in thyroid therapy.

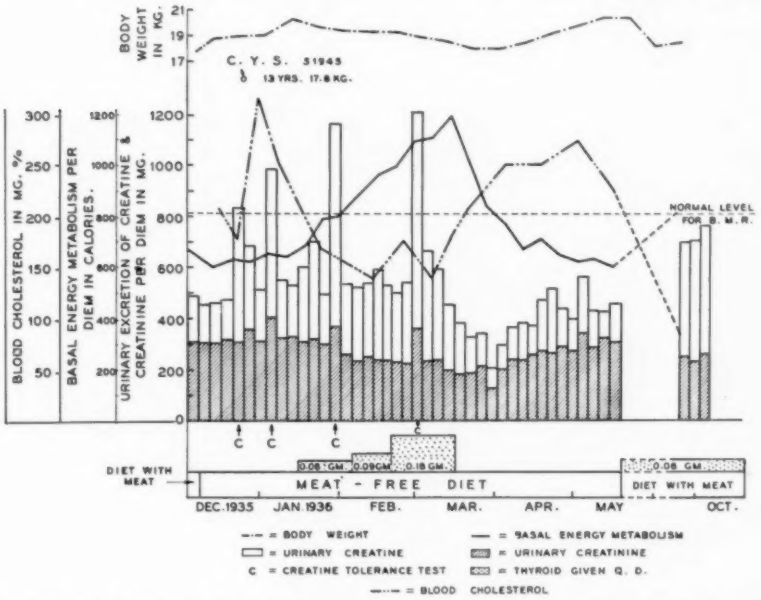

BODY WEIGHT IN KG.
C. Y. S. 51945
♂ 13 YRS. 17.8 KG.
BLOOD CHOLESTEROL IN MG. %
BASAL ENERGY METABOLISM PER DIEM IN CALORIES.
URINARY EXCRETION OF CREATINE & CREATININE PER DIEM IN MG.
NORMAL LEVEL FOR B. M. R.
C C C C
0.06 GM. 0.09GM. 0.18 GM.
0.08 GM.
DIET WITH MEAT
MEAT - FREE DIET
DIET WITH MEAT
DEC. 1935 JAN. 1936 FEB. MAR. APR. MAY OCT.
= BODY WEIGHT
= BASAL ENERGY METABOLISM
= URINARY CREATINE
= URINARY CREATININE
C = CREATINE TOLERANCE TEST
= THYROID GIVEN Q. D.
= BLOOD CHOLESTEROL

Fig. 3.—C. Y. S. Body weight, blood cholesterol, basal metabolic rate, and daily excretion of creatine and creatinine in urine.

## URINARY CREATINE

According to Magee,[10] a normal boy 6 years of age excretes 75 per cent of endogenous creatine as such, and a boy of 9 years, 33 per cent. In the cases of hypothyroidism reported by Poncher, Visscher, and Woodward,[3] very little or no creatine was excreted. In the cases here presented, the average figures for creatine and creatinine excretion are shown in Table II. The total creatinine figures were all within normal

TABLE II

AVERAGE DAILY EXCRETION OF CREATINE AND CREATININE IN MILLIGRAMS PER KILOGRAM OF BODY WEIGHT*

| SUBJECT | TOTAL CREATININE | PREFORMED CREATININE | CREATINE AS CREATININE | CREATINE AS PERCENTAGE OF TOTAL CREATININE |
|---|---|---|---|---|
| *Diet With Meat* | | | | |
| W. S. T. | 35.5 | 20.5 | 15.0 | 43 |
| C. Y. S. | 27.7 | 17.4 | 10.3 | 37 |
| *Diet Without Meat* | | | | |
| W. S. T. | 26.7 | 19.1 | 7.6 | 28 |
| C. Y. S. | 24.9 | 16.6 | 8.3 | 33 |

*Days of creatine tolerance tests were exempted.

limits. Subject W. S. T. illustrated very well the importance of diet in the excretion of total creatinine and creatine in children, a point which is at times not emphasized. Furthermore, on a meat-free diet, W. S. T. and C. Y. S. excreted 28 per cent and 33 per cent, respectively, of total creatinine as creatine. These values cannot be considered too low for their chronologic ages, but they are definitely low for their bony ages. It seems more reasonable to compare the creatine excretion in hypothyroidism cases with those of children who belong physiologically, rather than chronologically, to the same age group.

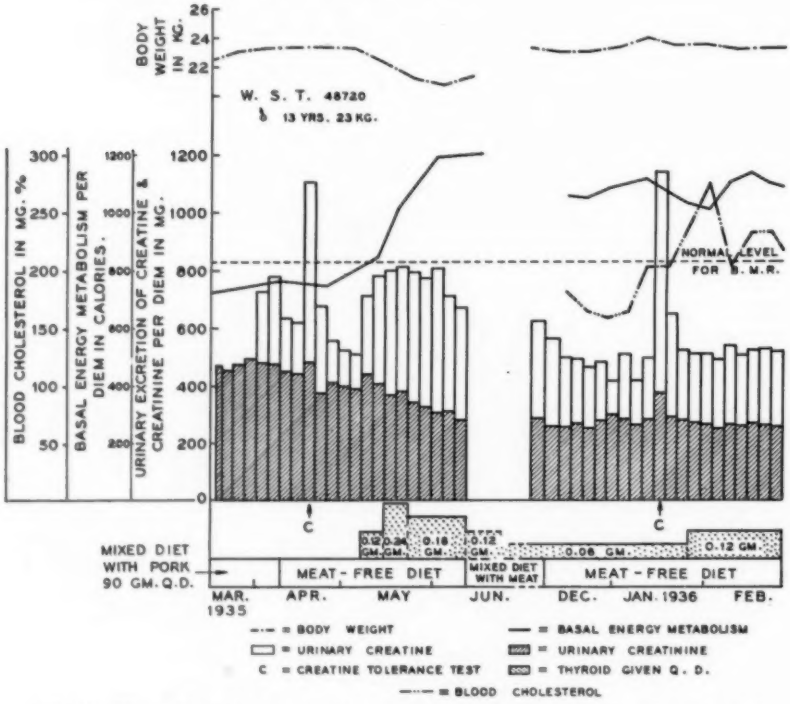



Fig. 4.—W. S. T. Body weight, blood cholesterol, basal metabolic rate, and daily excretion of creatine and creatinine in urine. (Urinary creatine was not determined before March 2, 1935.)

When thyroid was given, there was a prompt and marked rise in the creatine excretion. This was observed when thyroid was given for the first time, as in the cases of W. S. T. and C. Y. S., as well as in the previously treated case, T. A. N. The last case had been treated previously, so that at the time of study her basal metabolic rate was already normal. With the readministration of the dried gland, her basal metabolic rate further increased; a marked augmentation of creatinuria was also noted. This increase amounted to two or three times the value before medication.

As the therapy continued, however, it became clear that in all three cases the rise in creatine excretion was not parallel with the changes in basal metabolic rate. Like blood cholesterol, creatinuria may serve as a general index of thyroid effect, but cannot serve as a guide indicating the extent of the therapeutic action.

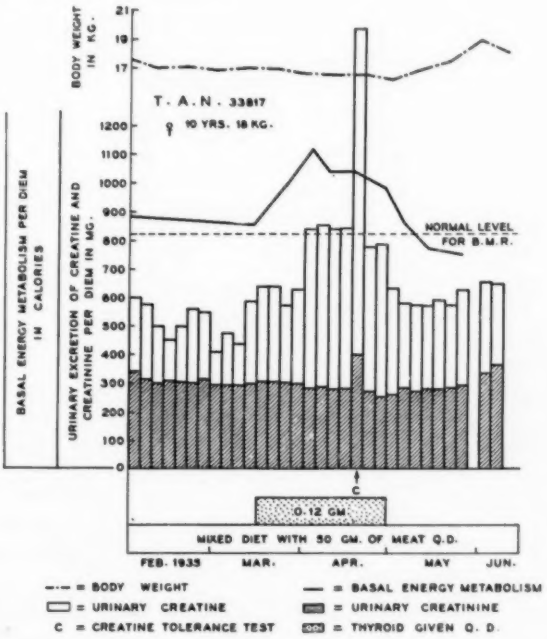



Fig. 5.—T. A. N. Body weight, basal metabolic rate, and daily excretion of creatine and creatinine in urine.

That this increased creatinuria is not due to the increased formation of creatine is evident from the above-mentioned work of Bodansky.[4] It is well established that the phosphocreatine in the muscles breaks down during contraction. For its resynthesis, energy is furnished chiefly by the degradation and oxidation of muscle glycogen. It was shown by Brentano[11] and Abelin and Spichtin[12] that thyroid medication also causes a decrease in muscle glycogen. The creatinuria following thyroid medication may then be looked upon as the result of the diminished capacity of the muscles to utilize creatine, in the absence of immediately available glycogen.

## CREATINE TOLERANCE TEST

That this augmented creatinuria is the result of decreased storage of creatine rather than its increased production can be seen further from the fact that continued thyroid medication did not result in a sustained

high level of urinary creatine. On the other hand, the decrease of tolerance, or the capacity of storing creatine, is well brought out by the creatine tolerance tests.

TABLE III

TOLERANCE OF NORMAL AND THYROID-DEFICIENT CHILDREN TO ORAL ADMINISTRATION OF CREATINE

| SUBJECT | AGE (YR.) | WEIGHT (KG.) | EXCRETION IN FIRST 4 DAYS* PERCENTAGE OF INTAKE | EXCRETION IN SECOND 4 DAYS* PERCENTAGE OF INTAKE |
|---|---|---|---|---|
| *Normal Children* | | | | |
| Chiang | 3 | 13 | 80 | 20 |
| Wang | 7 | 15.5 | 65 | 10 |
| Li | 8 | 24 | 50 | 10 |
| *Hypothyroidism Before Treatment* | | | | |
| W. S. T. | 13 | 23 | 65 | 10 |
| C. Y. S. (1st test) | 13 | 18 | 50 | 30 |
| (2nd test) | | 18 | 60 | 10 |
| *Hypothyroidism After Treatment* | | | | |
| W. S. T. | | | 90 | 20 |
| C. Y. S. (1st test) | | | 90 | 5 |
| (2nd test) | | | 90 | 20 |
| T. A. N. | | | 90 | 0 |

*One gram of creatine was given each day only during the first four days.

The determination of creatine tolerance in children is less reliable than in adults, who normally do not excrete endogenous creatine in the urine. There the presence of exogenous creatine may be measured accurately. With children who are excreting normally varying amounts of endogenous creatine from day to day, we can estimate only roughly the exogenous creatine that is excreted over the estimated average daily endogenous amounts. In the literature it is found that single determinations were made before and after the administration of creatine, to estimate the excretion of exogenous creatine, with the assumption that the endogenous creatine excretion is fairly constant from day to day. Such an assumption is unwarranted in view of the finding of marked fluctuation in the endogenous creatine excretion. This fluctuation would be even more marked if the diet had not been rigidly controlled. The average value of four to eight days before the administration of creatine was used here as a rough estimate of the level of endogenous excretion. Our results are shown in Table III. In these tolerance tests we administered creatine for four successive days instead of giving a single dose, as is usually done, in order to eliminate as much as possible the effect of daily fluctuations. The large total dose given also helped to bring out the effect of creatine feeding on creatinine excretion, which will be discussed later. On the other hand, this departure from the usual procedure precludes a comparison of our data with those reported by others. It is felt, however, that such a comparison of data from this country with those from the West would be of lit-

tle value, in view of the great difference in the usual diet, the physical development, and the degree of maturity of the musculature between groups of comparable ages.

Among the normal children, it is shown in Table III that the tolerance increases with age. The patients with hypothyroidism before treatment had a tolerance distinctly less than one would expect from their chronologic age. They excreted about the same amounts of administered creatine as one would expect from children of their bony ages. After treatment their tolerance was distinctly lowered. It is also of interest to note that the total estimated extra excretion might at times be more than the amount administered. This discrepancy may amount to 10 per cent. This simply shows that our estimate of the endogenous excretion of creatine is inaccurate to that extent, despite the fact that average values of a number of days have been used. Estimates based on single day determinations must be still more liable to error.

### URINARY CREATININE

In all three cases, a decided decrease of creatinine excretion was noticed during the course of thyroid treatment, particularly in cases W. S. T. and C. Y. S., who were on meat-free diets. In the case of T. A. N., who was on a diet with meat, this change was less marked, but still definite. This effect was in striking contrast with the usual reports: that is, no effect was usually said to be present in creatinine excretion on thyroid treatment.

TABLE IV

CHANGES IN BODY WEIGHT AND DAILY CREATININE EXCRETION DURING AND AFTER THYROID TREATMENT

| SUBJECT | BEFORE TREATMENT | | DURING TREATMENT | | AFTER TREATMENT* | |
|---|---|---|---|---|---|---|
| | AVERAGE BODY WEIGHT (KG.) | AVERAGE DAILY CREATININE EXCRETION (MG.) | MAXIMUM LOSS IN WEIGHT (KG.) | MAXIMUM LOSS IN CREATININE EXCRETION (MG.) | MAXIMUM GAIN IN WEIGHT (KG.) | MAXIMUM INCREASE IN CREATININE EXCRETION (MG.) |
| W. S. T. | 23.2[a] | 402[a] | 2.9 | 120 | — | — |
| C. Y. S. | 20.0[b] | 329[b] | 1.9 | 129 | 0.7 | 60 |
| T. A. N. | 16.9[c] | 306[c] | 0.6 | 50 | 2.6 | 107 |

*Increase as compared to the period during treatment.
[a]April 26 to May 7, 1935.
[b]Jan. 8 to Jan. 16, 1936.
[c]Feb. 1 to March 17, 1935.

Creatinine formation and excretion are supposed to be proportional to the amount of active tissue in the body; therefore, the first obvious possibility is that this decrease might be a result of the loss of muscular tissue during the thyroid medication. Although a loss of body weight did occur in each case with the administration of thyroid, the decrease of creatinine excretion was proportionately greater. This is shown in Table IV. It is evident that there was more decrease in creatinine ex-

cretion than can be explained by the losses in body weight, even with the assumption that the losses in active protoplasmic mass were in proportion to the inert tissues, such as water, fat, and myxedematous tissue, during the thyroid treatment. Further, during part of our study, S. H. Liu and his co-workers were studying the nitrogen balance on the same subjects. He has kindly supplied us with the pertinent data in Table V. It is seen that, even though the entire loss of nitrogen be attributed to that of the muscular tissue, which was most unlikely, the decrease in creatinine was still far too great. The case of T. A. N. is particularly striking. During the course of thyroid treatment she actually gained 31 Gm. of nitrogen from April 2 to 29. Yet the daily creatinine excretion actually diminished during the same period. On the discontinuance of the thyroid medication, the urinary creatinine returned to a higher level. Even though the body weight (active tissue) increased at the same time, the increase in creatinuria was again out of proportion to the increase of weight. It is clear, then, that this decrease is not due to a loss of active body tissue, but is due to the depletion of body creatine following the administration of the thyroid.

TABLE V

NITROGEN BALANCE AND CHANGE IN CREATININE EXCRETION

| SUBJECT | DATE | NITROGEN BALANCE (GM.) | DECREASE IN DAILY CREATININE EXCRETION | | THYROID TREATMENT |
|---|---|---|---|---|---|
| | | | AMOUNT (MG.) | PERCENTAGE | |
| W. S. T. | April 10 to May 7 | - 9.50 | ± | ± | 0 |
| | May 7 to June 12 | -96.71 | 160 | 36 | + |
| C. Y. S. | Dec. 15 to Jan. 15 | -23.11 | ± | ± | 0 |
| | Jan. 16 to Feb. 20 | -31.37 | 70 | 22 | + |
| T. A. N. | April 2 to April 29 | +30.92 | 30 | 7 | + |

It has been pointed out that creatinine formation is influenced by the availability of creatine in the body. Therefore, such a decrease of creatinine might be explained by a creatine deficiency. Such a deficiency was to be expected from the administration of thyroid combined with the use of a meat-free diet. Therefore, in the case of T. A. N., who was on a meat-containing diet, the decrease in creatinuria on thyroid therapy is much less marked.

That such an effect of thyroid on creatinine excretion has not been generally recognized by previous workers may be due to the following factors: (1) The metabolic studies might not have been carried out for long enough periods. In our cases the point of maximum decrease was not reached until more than one month after the administration of thyroid. (2) The diets might contain large amounts of creatine, as in our case of T. A. N., so that the depletion of tissue creatine was absent or minimal. Such is the case in the study of Poncher, Visscher, and

Woodward.[3] They used an ordinary meat-containing diet so that their results might be more applicable to clinical studies. A meat-free diet perhaps approximates more closely, however, the usual diet of the majority of our hospital patients.

Believing that the muscle mass is a better standard, particularly in children, in the study of the basal metabolic rate, Talbot[13] proposed to express the caloric output in terms of the creatinine in the urine. The rationale may be summarized thus:[14] "The experiments of Chanutin, and Benedict and Osterberg definitely established the origin of urinary creatinine from creatine. The excretion of creatinine parallels the amount of creatine in the body or (for practical purposes) in the muscles, because 98 per cent of the total creatine in the body is in the muscles. If this is admitted, it follows as an obvious corollary that, so long as the muscles possess a constant creatine content, urinary creatinine is proportional to muscle mass." Thus the following assumptions were implied: (1) that the amount of creatinine in the urine is not affected by exogenous creatine in the food; (2) that the muscle possess a constant amount of creatine content; and (3) that the excretion of creatinine parallels the amount of creatine in the body. That these assumptions are justified, in general, is not questioned. But, for the practical application of this principle, it is important to examine how completely these conditions are satisfied in a quantitative way.

It is true that in short feeding experiments, small amounts of ingested creatine apparently do not affect the creatininuria, because the metabolic process by which creatine is converted into creatinine is the slowest known to occur. Yet, if larger doses are used, as in our tolerance tests (see Figs. 3, 4, and 5), or if small amounts are fed for a longer period of time,[2] creatinine excretion is definitely increased. The amounts of creatine which we used in the tolerance tests were equivalent only to a little over 200 Gm. of meat and could have been taken as a part of the diet, if the latter had not been controlled.

Hunter,[15] summarizing the data on the creatine content in the skeletal muscles, concluded: "On a general survey of the data in Table II, it appears that among individuals of any one species chosen at random, the creatine concentration in the muscles varies within limits that are frequently rather wide." For man the listed results from four different authors showed a variation from 270 to 411 mg. per cent. The figures from individual authors had a smaller, but still appreciable, range. Further, the body content of creatine may be markedly affected under special circumstances. It may be increased after amino-acetic acid treatment,[16] or decreased after thyroid therapy[11] or in severe scurvy.[17] With regard to the quantitative parallelism between the creatine content of the body and the creatinine in the urine,

direct evidence is lacking. On the other hand, in children on a constant diet, the daily variation of creatine in the urine does not always parallel that of creatinine. Benedict and Osterberg[2] stated, "Our experiments seem to demonstrate almost conclusively that creatinine is but one of the end products of creatine metabolism." It is not known what are the factors which control the proportion of creatinine-forming creatine.

TABLE VI

DAILY EXCRETION OF CREATININE IN URINE OF NORMAL PERSONS (DATA FROM FOLIN)

| SUBJECT | NO. OF DETERMINATIONS | DAILY CREATININE EXCRETION | | DIET |
|---|---|---|---|---|
| | | MEAN (GM.) | RANGE (MG.) | |
| J. H. B. | 5 | 1.57 | 1.47-1.70 | Constant |
| E. H. S. | 5 | 1.46 | 1.41-1.50 | Constant |
| R. L. J. | 5 | 1.57 | 1.45-1.67 | Constant |
| G. E. C. | 5 | 1.77 | 1.67-1.88 | Constant |
| M. H. | 5 | 1.36 | 1.31-1.50 | Constant |
| S. R. B. | 5 | 1.58 | 1.53-1.64 | Constant |
| E. V. S. | 10 | 1.17 | 1.02-1.28 | Variable |
| S. F. | 14 | 1.49 | 1.33-1.66 | Variable |
| H. B. H. | 12 | 1.55 | 1.36-1.65 | Variable |
| E. S. A. | 13 | 1.14 | 1.05-1.22 | Variable |
| Aug. H. | 13 | 1.36 | 1.28-1.48 | Variable |
| O. F. | 16 | 1.56 | 1.32-1.77 | Variable |
| H. B. H. | 16 | 1.81 | 1.66-1.90 | Variable |

Theoretical considerations aside, a practical question is how constant is the creatinine content in the urine of a given individual. A casual perusal of the literature leads one to believe that the constancy is such that, by it, one may check even the completeness of daily urine collections. Yet Hunter stated clearly in his monograph:[15] "The constancy which it [creatinine] asserts must, it is true, be allowed to be something short of absolute. In the figures of Table XI, there may be observed differences in the daily output of a single individual which at times amounts to more than 10 per cent of his average; and, if the data scattered throughout the literature are all to be depended on, still greater variations are normally possible. Schulz, for example, reports that his minimum daily output during an eleven-day period of strictly meat-free diet, was 23.7 per cent below his maximum. Zwarenstein concludes, from observations on four individuals, that the daily excretion shows marked variations and is not remarkably constant as had been supposed." As a matter of fact, one has only to inspect the figures in the original papers of Folin[1, 18] to see that significant daily variations did occur (Table VI). Marples and Levine[19] pointed out that this constancy of creatininuria is even less striking in infants and children than in adults. In Table II of their article it may be readily seen that, for a given individual, the creatinine excretion might easily vary over 10 per cent during a short experimental period, during which significant change

in the body composition could not have occurred. Our experience in this study, as well as in the study of normal cases,[20] also bears out this statement. The excretion of creatinine is also affected by endocrine secretions. We have discussed the influence of the thyroid. Prolan[21] is stated to diminish creatininuria. Antuitrin G and the secretion of eosinophilic tumors increases creatininuria; acromegalics also excrete much endogenous creatinine in amounts which vary from day to day.[22] It is clear, therefore, that further studies are necessary before basal metabolic rates can be expressed confidently in terms of urinary creatinine, especially when the diet is not controlled and only single determinations of daily creatinine excretion are made.

## SUMMARY

Three cases of hypothyroidism were studied. It was shown that the level of blood cholesterol gave a general indication of the therapeutic effect of thyroid, but did not serve as a reliable quantitative indicator of the basal metabolic rate. The degree of creatinuria also did not parallel the level of the basal metabolic rate, either before or after thyroid therapy.

On the institution of thyroid therapy, there was a prompt and marked increase of creatinuria. This creatinuria was not due to the increased production of creatine, but rather was the result of the decreased capacity of the body tissues to store or utilize the substance. This is shown by the results of the creatine tolerance tests. It is suggested that such an intolerance might be due to the decreased availability of muscle glycogen.

The urinary creatinine showed definite tendency to decrease as the thyroid therapy was continued, especially when the subject was on a meat-free diet. It is shown by the simultaneous studies on body weight and nitrogen metabolism that such a decrease could not have been due to the loss of active body tissue. It is pointed out that such a decrease must be due to the depletion of creatine in the tissue on account of the exaggerated creatinuria during the course of thyroid therapy. This is further supported by the fact that the amount of urinary creatinine temporarily increased when extra creatine was given during the creatine tolerance tests.

This decrease in creatininuria following thyroid therapy is contrary to the usual reports, but fits in logically with the conception that creatinine is derived from creatine in the body.

Theoretical limitations to the use of urinary creatinine as a standard of basal energy metabolism are discussed. It is emphasized that the constancy of daily creatinine excretion is only relative, and that it may be influenced by factors other than thyroid as reported here.

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# THE TREATMENT OF GRAVES' DISEASE IN CHILDREN

NORMAN NIXON, M.D.
LOS ANGELES, CALIF.

THE majority of reports[1-14] in the literature discussing the treatment of Graves' disease are based upon the experiences of large surgical clinics and emphasize the operative treatment of this condition. On the other hand, studies based upon the nonsurgical treatment[15-22] of hyperthyroidism in selected cases, although in the minority, are none the less convincing. While the results of subtotal thyroidectomy are satisfactory in many instances, the operative mortality, low as it is, together with various complications and sequelae and the not infrequent failure to cure the condition following operation,[23] should be considered carefully before assuming that surgery is an ultimate requirement in treating every instance of Graves' disease.

In the adult the occasional postoperative occurrence of myxedema, although undesirable, can be controlled by adequate administration of desiccated thyroid, and other complications of thyroidectomy usually are amenable to treatment. In the child, however, the relationship of the thyroid to the other endocrine glands and the all-important part which it plays in the normal processes of growth and development, both mental and physical, should make its removal undesirable if it is possible to treat Graves' disease in children without operation.

## AGE AND DISTRIBUTION

Graves' disease occurs rarely before puberty. Statistics from large surgical clinics indicate that less than 1 per cent of all patients treated for this condition are children. When it does occur, the symptoms and findings are essentially the same as in the hyperthyroid adult. While proved instances of hyperthyroidism have been reported in children under 5 years of age,[2, 6, 25-28] the majority of cases occur in the prepuberty and early adolescent years. The same sex difference is observed in children as in adults, girls being affected at least three times more frequently than boys.

Graves' disease has been observed in every land and climate and in nearly every race. A recent study[29] has demonstrated that exophthalmic goiter is more generally distributed throughout the United States than is simple goiter, occurring in some regions where the latter is unknown, and suggests that each of these two types of goiter has an independent etiological background. The incidence of thyrotoxicosis is much greater in large cities than in small rural communities, from which fact one may conclude that the added nervous tension of urban life, with its ever-increasing excitement, competition, hurry, and struggle, is an important factor in precipitating the disease in persons born

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with the constitutional background. The same type of person living an easygoing existence in a more sheltered environment might not be subject to the disease.

### MEDICAL TREATMENT

Granting that the cause of Graves' disease is still unknown and that the thyroid gland plays an important part in the normal growth and development of the child, it would seem advisable to attempt to treat this condition conservatively when it occurs before adolescence. At least, the hyperthyroid child should be subjected first to a carefully planned and executed medical regime.

To provide complete physical rest, the patient should be put to bed. Mental rest is as important for the child, as for the adult, with exophthalmic goiter. If possible, the causes of the emotional disturbances, which often precipitate the acute symptoms, should be removed. To do this, it is necessary in most instances to remove the child temporarily from his home and family associations. Certainly, however, the hospital does not provide a suitable environment for the peace and quiet so essential to these patients. The constant flow of activity in a children's ward, with the daily excitement of numerous contacts with nurses, interns, attending men, technicians, medical students, etc., is not conducive to complete rest. After the diagnosis has been confirmed by the various required laboratory procedures, the child should be sent, when it is possible, to a suitable convalescent or boarding home where the rest regime can be continued as long as there is improvement in his condition. Psychotherapeutic measures and an individualized approach to each patient's problem are important in the medical treatment.

The diet should be well balanced and high in caloric value, to avoid weight loss due to the increased oxidation. Although proteins usually are restricted in the diet for the hyperthyroid adult, the protein needs for normal body growth must be provided in the child's diet despite the high specific dynamic action of protein foods and their tendency to stimulate the thyroid. The addition of various vitamin preparations is advisable.

In many instances, the acute symptoms subside only with the complete disappearance of the inciting infection. Abscessed teeth, infected tonsils, and other foci should be removed if the child's condition warrants, but not until he has shown considerable improvement.

Various gland preparations have been recommended, but their efficacy in children has not been proved. Sedatives, especially the barbiturates, serve a useful purpose in calming the patient during the acute stage.

By giving small doses of iodine,[19, 24, 30, 31] one can lower the increased metabolic rate, with a corresponding gain in the child's weight and improvement in his general condition. Iodine, however, is a drug to be respected and should be used with caution in the treatment of hyperthyroidism. It has a place in the conservative treatment, but when it is used, one should be prepared to advise thyroidectomy at the proper

time if the patient's response is not optimum. Mild cases of Graves' disease usually do not require iodine, responding adequately to the conservative regime if adhered to judiciously and patiently over a fairly long period of time. In the moderate and severe cases, however, iodine is a most helpful adjunct in the treatment, but its use should be postponed until one is certain the patient will not improve without it. With iodine, the oxygen requirements of the tissues are diminished markedly, many times to a normal level, so that the demand for thyroid hormone is reduced.

It is well to point out that Lugol's solution usually prescribed in the United States is five times the strength of that employed abroad, containing 5 per cent iodine and 10 per cent potassium iodide, in contrast to 1 per cent iodine and 2 per cent potassium iodide in the weaker solution.[24] It is possible that this marked difference in strength may explain the frequent warnings of American surgeons[32] who advise the use of iodine only as a preoperative measure. The use of the weaker solution would seem to hold an advantage, for it is safer, can be used over a longer period of time, and, in most instances, with smaller doses than those advocated for the U.S.P. preparation, will cause improvement in the patient's subjective symptoms as well as in his general condition. A recommended course is to give from 5 to 6 drops three times daily for approximately ten days and then to reduce the amount of drug to 1 to 3 drops three times daily, increasing it again temporarily if the dose should seem inadequate.

American surgeons are the chief advocates of large doses of iodine, given only for a limited time, however, when preparing patients with exophthalmic goiter for operation. The postoperative reaction which occasionally follows thyroidectomy probably is due to hypothyroid shock inasmuch as the blood iodine content in these patients is diminished.[33, 34] Previously it was thought the crisis was due to an increased excretion of thyroid hormone following the manipulation of the thyroid during surgery. To avoid this reaction, surgeons now usually increase the iodine dosage on the days immediately preceding and following thyroidectomy.

Some writers[32] have argued that long-continued administration of iodine makes the patient "iodine-fast" by increasing his tolerance for the drug, so that, should surgery become necessary, the optimum effect of the iodine remission will be lost. Many clinicians, however, believe such a view is erroneous and advocate small doses of iodine as a part of the medical treatment of all but the very mild cases of Graves' disease. Often small doses of syrup of hydriodic acid or of weaker Lugol's solution are well borne for many weeks, months, or even years, resulting in permanent relief of symptoms.

Even in some large surgical clinics recent reports[19] indicate that the percentage of cases treated by iodine alone is increasing, suggesting a greater effort to treat this disease medically rather than to consider all cases surgical.

### SURGICAL TREATMENT

Surgeons generally recommend subtotal thyroidectomy, following complete iodinization, for most cases of Graves' disease in children. When the course of the disease is progressive despite perseverance and patience in carrying out the conservative treatment, subtotal thyroidectomy will bring about alleviation of the toxic symptoms in most instances. However, one must remember that prolonged rest and medical care, usually with temporary iodine administration, are necessary, even following surgery.

Because the tendency to residual and recurrent thyrotoxicosis is greater in children than it is in adults, a very generous subtotal thyroidectomy usually is performed.[35] Some surgeons,[2, 36] however, believe a more conservative removal of thyroid tissue is advisable in the growing child, more so than in the hyperthyroid adult, so that there will be no question of myxedema developing. To prevent disturbance of the parathyroid glands, at least a portion of the posterior surface of both lobes must be left standing.

While the operation often is performed in one stage, many surgeons still advise two-stage thyroidectomy as the safest procedure, especially in all severe cases of thyroidism in children.

### IRRADIATION

Few reports are available on the use of x-ray in treating Graves' disease in children. Its use in adults still is debatable, although there are many favorable reports[37-40] in the literature. Some writers have pointed out such advantages as low mortality, lack of shock and serious complications, and low cost, with satisfactory results in as high as 65 per cent of adequately treated cases. It is recommended as an adjunct to iodine treatment when the improvement with iodine alone is not sufficient. In Means' clinic many instances of recrudescences in children are being treated by x-ray rather than by further surgical removal of thyroid tissue.

### EVALUATION OF THERAPEUTIC MEASURES

Before an intelligent opinion is possible concerning the efficacy of any therapeutic procedure used in treating Graves' disease in children, one must observe the patient for a number of years.[41] Too often impressions are based upon a brief period of observation and treatment with no systematic follow-up. Especially is this likely in large surgical clinics handling referred cases from many communities in wide sections of the country. Often, visits to the clinic are not practical following convalescence from surgery, so that further observations and follow-up reports must be made by the family physician whose experience with exophthalmic goiter in a child may be extremely limited.

While the immediate effect of subtotal thyroidectomy appears to be beneficial in many instances, in so far as the hyperthyroid symptoms

are concerned, it is difficult to predict changes in the future development of the child when the thyroid is removed before puberty. Will he, minus this tremendously important gland, grow and develop physically and mentally into a normal adult? Will fecundity be diminished, and if there are children, will they be more apt to show signs of hypothyroidism? Only when carefully controlled cases are observed for many years following thyroidectomy and irradiation, and when impartial statistics are made available, will we have satisfactory answers to these and many other questions concerning this problem.

## CASE REPORTS

During the last fourteen years (1926-1940) nine patients with Graves' disease were observed in the Los Angeles Children's Hospital. A brief outline of these cases follows:

CASE 1.—L. R., an 11½-year-old Italian boy, was admitted Jan. 15, 1927 (Fig. 1). There were six siblings. He had been nervous and losing weight for five months, but had an excellent appetite. Thyroid enlargement had been present four months.

Fig. 1.—L. R., Case 1, on admission to hospital.

Examination showed a thin, undernourished, extremely nervous boy with exophthalmos, diffuse enlargement of the thyroid, and fine tremor. Pulse was 120; blood pressure, 118/50; hemoglobin, 70 per cent; basal metabolic rate, +45 per cent (one determination).

*Treatment* consisted of Lugol's solution, 5 to 7 drops t. i. d., for three weeks. The pulse rate remained unchanged, but he gained 5 pounds and seemed improved. He

underwent three operations: the first, ligation of the right superior thyroid artery, March 2, 1927; the second, ligation of the left superior thyroid artery, March 9; and the third, subtotal thyroidectomy, March 23. Ethylene anesthesia was used. His condition was poor on leaving the operating table. There were marked cyanosis and tachycardia, with shallow respiration. He died several hours later.

*The autopsy report* (incomplete) was hyperplasia of the thyroid gland, with colloid infiltration.

CASE 2.—E. K., a 9-year-old girl was admitted Jan. 3, 1926 (Fig. 2). She had had measles at 6 months of age, and pertussis and mumps at 6 years. The father was ill; the parents and four children were supported by city charity. Thyroid enlargement had been present for four years, with rapid pulse and increasing nervousness for the past year. School attendance was impossible.

Fig. 2.—E. K., Case 2, three weeks after admission to hospital.

Examination showed marked diffuse thyroid enlargement, nervousness but no exophthalmos, and a "definitely elevated, probably +30 to +40 per cent" basal metabolic rate. Pulse averaged 120.

*Treatment* consisted of Lugol's solution, 10 minims t. i. d., for eighteen days. The girl lost 9 pounds during iodine treatment, but gained 3 pounds in the first three days after Lugol's solution was stopped. The pulse became more regular, but was still rapid. She was less nervous and had a good appetite after six weeks' bed rest.

Surgery (thyroidectomy) was refused. The child was taken to Aimee's Temple. There was no record of results, and the family moved away, so that follow-up was impossible.

CASE 3.—L. A., a 7-year-old Mexican girl, was admitted Nov. 8, 1933. Congenital dislocation of the hip had been treated successfully at 2½ years of age.

She was now undernourished and nervous, with slight thyroid enlargement, fine tremor, and tachycardia. No eye signs were evident. The basal metabolic rate was "unsatisfactory"; pulse was 110. An x-ray of the chest was negative.

*Treatment* consisted of tonsillectomy and adenoidectomy, and Lugol's solution, 5 minims t. i. d., for seven weeks. The pulse was reduced and she gained 3½ pounds. Fine tremor of the hands, slight exophthalmos, and thyroid enlargement were still evident. Improvement continued on a conservative regime.

Fig. 3.—L. A., Case 3, aged 13 years, six years after acute symptoms first became evident.

*Follow-up* shows that, at 13 years, weight and development are normal with normal menses for the past year. Thyroid enlargement is not evident. She is not nervous, and there is no tremor. Pulse is 80; basal metabolic rate, –5 (sitting height). (Fig. 3.)

CASE 4.—B. S., an 8-year-old girl, was admitted Oct. 3, 1930. Her paternal grandmother had had goiter. The patient had always been a nervous child, but was worse during the past two years, with emotional instability and change in disposition. Thyroid enlargement was present for four years. Slight dyspnea was experienced when lying down. She had a tremendous appetite, and perspired excessively.

Examination showed moderate thyroid enlargement, with bruit, slight exophthalmos, and fine tremor. X-ray examination of the chest showed "appreciable upper mediastinal density."

*Treatment* consisted of bed rest at home for one month without medication. On Nov. 1, 1930, she was admitted to a private hospital, with exophthalmos, thyroid enlargement, tremor, and nervousness unchanged. Basal metabolic rate was +30 per cent; pulse, 162. Lugol's solution, 5 to 10 minims was given t. i. d. for ten days.

A subtotal thyroidectomy was performed Nov. 12, under nitrous oxide-oxygen anesthesia. She was on the table fifty minutes. The patient died on the second postoperative day (thyroid crisis?).

*Autopsy* showed status thymicolymphaticus.

CASE 5.—S. M. B., a 7-year-old negro girl, was admitted May 29, 1933. Her father had diabetes. One sibling was well. The patient was nervous and losing weight despite a ravenous appetite.

Examination showed symmetrical thyroid enlargement, exophthalmos, and tremor. The basal metabolic rate was +23; pulse, 150; blood pressure, 114/60; hemoglobin, 67 per cent. X-ray examination of the chest showed "fullness of upper mediastinal shadow not exactly characteristic of thymus." There were several infected teeth and diseased tonsils. Urine was normal.

*Treatment* consisted of Lugol's solution, 3 to 5 minims, t. i. d., for two weeks. Two operations were performed, both under nitrous oxide and ether anesthesia: removal of the isthmus and most of the right lobe of the thyroid, July 26, 1933; removal of two-thirds of left lobe, Aug. 23, 1933. When discharged Oct. 4, 1933, her pulse was somewhat slower, and she was less nervous. Her weight was unchanged, but the general condition was improved.

She was readmitted three months later for tonsillectomy and adenoidectomy and died on the table during the first stage of ethyl chloride and ether anesthesia.

*Autopsy* showed status thymicolymphaticus. The thymus weighed 97 Gm. There were prominent mesenteric lymph nodes, etc.

CASE 6.—D. S., a 6½-year-old girl, was admitted Oct. 8, 1934 (Fig. 4). Her maternal uncle had had a goiter removed. The patient had had a tonsillectomy and adenoidectomy two years previously. She showed thyroid enlargement, especially

Fig. 4.—D. S., Case 6, one week before thyroidectomy.

of the right lobe, but no tremor. There were 59 per cent lymphocytes; basal metabolic rate was +32 (body surface). The "child was rather frightened during the test." X-ray of the chest was negative; urine was normal.

*Treatment* consisted of Lugol's solution, 5 to 10 minims t. i. d., for three weeks. The right lobe and isthmus were removed Nov. 17, 1934. The basal metabolic rate was −22 two weeks following surgery.

*Pathology* showed hyperplastic goiter.

The child was followed in the outpatient department and showed satisfactory progress until eleven months later when she was readmitted, with a typical picture of diabetes mellitus in severe acidosis. Blood sugar was 383 mg. An unexplained fever of 101 to 104° F. was present for two weeks before death one year after subtotal thyroidectomy.

*Autopsy* revealed diabetes mellitus, hemorrhagic enteritis and colitis, and multiple abscesses of the left kidney, with bilateral pyelitis. The thymus weighed 10 Gm.; only a thin sheet of tissue was left. Lymphoid tissue was prominent throughout the small and large intestines.

CASE 7.—P. T., an 11-year-old girl, was readmitted Nov. 27, 1939, four months after right nephrectomy for hydronephrosis and hydroureter. She had been nervous and irritable for two months, with palpitation, excessive perspiration, and night sweats. She was undernourished, although she had gained 8 pounds since nephrectomy.

Examination showed exophthalmos and slight thyroid enlargement. Blood pressure was 124/60; pulse, 140; urine, negative; phenolsulphonphthalein in urine, 65 per cent after two hours; hemoglobin, 73 per cent.

Fig. 5.—P. T., Case 7, after three months on conservative regime and one month prior to thyroidectomy.

*Treatment* consisted of bed rest, with a special diet containing vitamins, iron, etc. She gained 18 pounds in the three months prior to surgery. Pulse was down to 100 average. (Fig. 5.) She received iodine treatment (potassium iodide) for three weeks; Lugol's solution was administered for ten days. A subtotal thyroidectomy was performed Feb. 28, 1940, under avertin and cyclopropane anesthesia.

The patient was seen in the outpatient department March 8. Pulse was 88. There was slight tremor and the exophthalmos was unchanged, but her general condition was very satisfactory.

CASE 8.—B. A., a 10½-year old girl, was admitted Dec. 1, 1939. There had been thyroid enlargement for two years, but extreme nervousness, tremor, exophthalmos, and weight loss (10 pounds) during the past three months after two attempts by burglars to enter the family home through the child's room.

Fig. 6.—B. A., Case 8, on admission to hospital.

Laboratory findings showed: blood pressure, 138/55; pulse, 120; basal metabolic rate, +5 (sitting height); lymphocytes in blood differential, 47 per cent. X-ray examination of the chest was negative. A pansinusitis, with low-grade fever for two months, cleared with conservative treatment.

*Treatment* consisted of bed rest, high caloric diet, vitamins, etc. The pulse was down to 110. She was less nervous, and her weight was stationary. She received iodine treatment (potassium iodide) for three weeks; Lugol's solution, for two weeks. Two operations were performed, under avertin and cyclopropane anesthesia: subtotal thyroidectomy (right lobe), March 6, 1940; subtotal thyroidectomy (left lobe), March 13.

*Pathologic studies* showed well-formed acini filled with colloid, and areas of lymphoid and epithelial hyperplasia.

The girl was followed in the outpatient department. There was paralysis of left vocal cord with hoarseness for several weeks. Pulse was 130. She gained back weight lost while in the hospital. Her general condition improved, but she was still extremely nervous.

CASE 9.—J. M., a 12½-year-old girl, was seen in the outpatient department Jan. 26, 1939, suffering from extreme nervousness, physical exhaustion, and an occasional convulsive seizure. The mother had been treated for goiter since the age of 15.

Examination revealed moderate thyroid enlargement, with slight tremor, exophthalmos, and pulse averaging 120. Blood pressure was 129/69; basal metabolic rate, +27 (sitting height). There was no weight loss, and no catamenia. No cause for convulsions was evident after a complete neurologic study.

*Treatment* consisted of bed rest at home, diet, emmenin, and sedatives. Normal menstruation began after three months and has occurred regularly since that time. The patient gradually returned to school and normal life after three months' rest.

Fig. 7.—J. M., Case 9, one year after acute symptoms were first observed.

One year later the basal metabolic rate was +6; pulse, 88. She was not nervous, and was on the honor roll at school, with many extracurricular activities. She seems quite normal mentally and physically, except for very slight exophthalmos and slight thyroid enlargement. She still has an occasional attack resembling petit mal.

## DISCUSSION

While one cannot draw conclusions from such a small series, these case reports illustrate some of the points mentioned earlier. Only eight of the cases can be considered inasmuch as one child could not be followed. Of the eight, two were treated conservatively and, while their symptoms were mild, both made complete recoveries. The remaining six patients were operated upon, with four deaths registered within one year following surgery. Two died within two days following thyroidectomy; another death occurred three months later during administration of an anesthetic prior to tonsillectomy and adenoidectomy; the fourth child died in diabetic coma twelve months after the subtotal thyroidectomy, having had no manifestations of diabetes before her terminal illness, which lasted approximately one

month. The other two surgical cases were operated upon within the last six months, and while both children have shown some improvement, not enough time has elapsed to evaluate the effects of surgery. One of the latter patients showed paralysis of the left vocal cord, with hoarseness, following thyroidectomy.

While true diabetes occurs infrequently in association with hyperthyroidism, pre-existing diabetes is aggravated by a complicating picture of Graves' disease,[42] the insulin requirement being increased materially. A previously latent diabetes will become clinically active as a result of hyperthyroidism. In these diabetic patients with exophthalmic goiter, the effect of iodine administration is almost as striking as that of giving insulin, and thyroidectomy usually is followed by improvement in the diabetic picture. Although Case 6 showed no outward evidence of diabetes until eleven months following the thyroidectomy, it is possible that the hyperthyroidism caused a flare-up of a previously latent diabetes, that the thyroidectomy produced a temporary improvement in the condition, and that the severe pyelonephritis with multiple abscesses in the left kidney, causing the febrile reaction of the terminal illness, was the etiological factor in breaking down the tolerance and precipitating diabetic coma.

At autopsy, findings consistent with those characteristic of status thymicolymphaticus were observed in three of the four deaths in this series. In the fourth patient (Case 1), the complete autopsy record is not available. In each of the three patients there was some evidence of generalized lymphoid hyperplasia, especially of the lymph nodes, Peyer's patches, and solitary lymph follicles of the intestinal tract. Two of the three patients had marked hypertrophy of the thymus; the third patient, who died in diabetic coma one year following thyroidectomy, had a very small thymus, even though there was evidence of lymphoid hypertrophy elsewhere. It is possible that some months following thyroidectomy and the resulting clinical cure of Graves' disease the thymus atrophies, there being no further need for its antagonistic action to the enlarged and overworked thyroid.

Eight of the nine patients were girls, and the ages varied from 6½ to 12½ years, there being four over 10 years of age. All but one of the nine patients were admitted through the clinic and came from homes of meager circumstances. Most of these children came from large families, with the increased nervous tension due to many persons living in small quarters with an insecure and inadequate economic background. There was a family history of goiter in only three instances.

In one patient the onset of her hyperthyroid symptoms definitely followed the severe emotional shock resulting from two attempts to burglarize the family home through the child's room. Another patient's symptoms began two months after a major operation (nephrectomy), although there was no immediate postoperative shock. In the majority of instances, however, the onset was more gradual.

## CONCLUSIONS

The etiology of Graves' disease is still unknown. However, Warthin's theory[43] of a Graves' constitution seems tenable in view of pathologic and autopsy findings and is based upon the existence of a thymicolymphatic background in most instances of true exophthalmic goiter, with the thyroid changes but one manifestation of the general picture.

Because the thyroid probably is not the primary pathogenic factor and because it plays a tremendously important part in the growth and development of the normal child, it would seem advisable to treat Graves' disease in children on a conservative basis. Thyroidectomy should be performed only on those children who do not show definite improvement after a comparatively long period of treatment on a carefully planned and executed medical regime.

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1136 WEST SIXTH STREET

# A CASE OF PICK'S SYNDROME AS THE BASIS FOR A STUDY OF HYPOPROTEINEMIA

HAROLD STADLER, M.D., AND DOROTHY STINGER
IOWA CITY, IOWA

A CASE of Pick's syndrome has furnished the basis for a study of the factors involved in the origin of low serum proteins in persons suffering from hepatic disease. That hepatic disease is frequently associated with hypoproteinemia is a matter of common knowledge. The mechanism of depression of the plasma proteins, however, continues to elude the great number of investigators who have interested themselves in this problem.

E. S. was thirteen years old when first observed on Aug. 14, 1939. He was brought in because of abdominal distention and shortness of breath, which had begun rather insidiously about three years previously. At that time he had gradually lost energy, and his appetite had decreased. Stiffness of the neck had developed, but this had been relieved by thoracentesis. A biopsy of a cervical lymph node done shortly afterward was reported as showing "chronic hyperplasia." About one month later the abdominal swelling became more severe, and paracentesis was done with the evacuation of approximately eight pints of pinkish-green fluid which was serous in nature. Following this the patient required abdominal tapping weekly for two months. Dyspnea had been markedly relieved by removal of fluid from the abdominal cavity. Jaundice had not occurred. There had been increased urinary frequency during the day. No further taps were done until three weeks before he was seen here.

Respiratory oppression of grade corresponding to the degree of abdominal ascites was the patient's only complaint; the marked edema of the lower extremities had occasioned little discomfort; and the boy was fairly active and was even attending school. It was said that his diet during his entire illness had been complete, and that his appetite had been good. No infection had preceded the onset of his disease. The only childhood illness that could be recalled was measles, which was contracted when the boy was nine years of age and which was uncomplicated.

Physical examination revealed the weight to be 121 pounds, height, 57 inches, and temperature, 102.6° F. The body was asymmetrical because of marked abdominal swelling and edema of the lower extremities. The face, chest, and the upper extremities were atrophic. There were dilated veins on the temples and forehead as well as on the abdomen. The costal margins moved asymmetrically and cephalad on respiration; the diaphragms were elevated; and there was evidence of pleural effusion on both sides. Rhonchi could be heard through both lung fields though breath sounds were suppressed over both bases. The size of the heart could not be estimated; the tones were soft; and there was no murmur. The rhythm was tic-tac in type. Blood pressure was 115 millimeters of mercury systolic and 75 diastolic. The pulse was small, and the rate, rapid. The abdomen was distended to such a degree that palpation of organs was not possible until after paracentesis. It was found that the liver and the spleen were very large, the liver approximating the umbilicus, and the spleen, the iliac crest. The organs were smooth to touch. There was suggestive acropachy. Reflexes were generally hypoactive; none was pathologic. Internal and external hemorrhoids were present.

From the Department of Pediatrics, College of Medicine, State University of Iowa.

The urine was alkaline and had a specific gravity of 1.030; tests for albumin, sugar, and blood were negative. The total leucocyte count was 13,000, and the erythrocyte count, 5,000,000 for each cubic millimeter of blood. The hemoglobin was 13 Gm. for each 100 c.c. of blood (Haden-Hauser).

Plasma cholesterol was 144 mg.; sugar, 89 mg.; and nonprotein nitrogen, 39 mg. for each 100 c.c. of blood. Total plasma protein was 4.2 Gm. per 100 c.c. of plasma with partition of albumin, 1.7 Gm., globulin, 2.3 Gm., and fibrinogen, 0.2 Gm. The icteric index was 6 units (bilirubin concentration not increased); serum phosphorus, 5.8 mg.; and serum phosphatase, 22 Jenner-Kay units for each 100 c.c. of blood (all values normal except the phosphatase and albumin levels); unfortunately the serum calcium determination was not satisfactory.

Examination of the ascitic fluid showed it to be alkaline and to have a specific gravity of 1.008. The nonprotein nitrogen concentration was 30 mg.; protein, 0.48 Gm.; and the sugar, 121 mg. for each 100 c.c. of fluid. Cholesterol was absent. No cells were found after a specimen was centrifuged.

Agglutination tests for Malta fever, typhoid fever, and the dysentery group were negative as were the Wassermann test and the tuberculin test; the latter test was repeated in a concentration of 1:100, and a negative result obtained.

The patient returned to the outclinic at weekly and biweekly intervals for observation. Treatment consisted of periodic removal of ascitic fluid and subsequent intravenous therapy with whole blood, plasma, or a solution of amino acids.* A high protein diet was administered. The therapy and average blood protein values for each month of the study are shown in Table I. The 3,250 c.c. of whole blood which the patient received under our care would furnish 114 Gm. of protein. The 8,500 c.c. of human plasma administered intravenously would furnish 525 Gm. of protein. The total would be approximately 700 Gm. of protein. On the other hand, abdominal paracentesis yielded somewhat more than 50,000 c.c. of ascitic fluid. When an average of the protein content of various samples of the fluid is taken, it can be roughly estimated that the patient lost little more than 165 Gm. of protein by this route. The plasma albumin of the patient remained consistently low, notwithstanding the ingestion of a diet fairly rich in protein and a total of ap-

TABLE I

| MONTH | FLUID REMOVED BY PARACENTESIS* (C.C.) | INTRAVENOUS THERAPY CARRIED OUT | | | GM. FOR EACH 100 C.C. OF PLASMA | | | |
|---|---|---|---|---|---|---|---|---|
| | | WHOLE BLOOD (C.C.) | AMINO ACID 10% (C.C.) | PLASMA† (C.C.) | T. PRO. | ALB. | GLOB. | FIBR. |
| Aug. | 5,600 | 750 | | 750 | 3.5 | 1.25 | 1.9 | 0.4 |
| Sept. | 6,000 | 1,000 | 200 | 1,750 | 3.8 | 1.50 | 1.9 | 0.4 |
| Oct. | | | 400 | 1,250 | 4.2 | 1.8 | 1.8 | 0.6 |
| Nov. | 6,000 | 500 | 100 | 1,000 | 4.3 | 1.4 | 2.3 | 0.6 |
| Dec. | 10,000 | 500 | | 1,000 | 4.3 | 1.5 | 2.4 | 0.3 |
| Jan. | 11,500 | 500 | | 500 | 4.4 | 1.6 | 2.3 | 0.5 |

*An amount of ascitic fluid estimated to be 12,000 c.c. was removed by the referring physician. The protein content of the fluid varied in different specimens from 0.21 to 0.48 Gm. for each 100 c.c. of fluid. The average protein content was 0.34 Gm. for each 100 c.c.

†Not including lyophile serum used.

*Provided through the courtesy of Mead Johnson and Co.

proximately 500 Gm. of serum protein introduced intravenously over and above the loss in ascitic fluid. Some small rise in globulin occurred, apparently compensatory, but the total protein remained always below 4.5 Gm. per 100 c.c. of serum.

A study was therefore undertaken to determine whether the protein ingested could be utilized. The protein intake was made very large in order to put strain upon the mechanism for catabolism. The data are shown in Tables II and III. The child was able both to absorb and retain protein in ample amount. The distribution of urinary nitrogen components was within normal limits for a child of his age. The child was thus able to absorb, retain, and catabolize protein normally, yet was utterly unable to maintain plasma albumin at its normal level, even though ample building components were available.

TABLE II

NITROGEN BALANCE STUDIES

| TOTAL NITROGEN | |
|---|---|
| PLACE FOUND | GM./DAY |
| Intake | 29.98 |
| Urine | 22.70 |
| Feces | 2.98 |
| Total excretion | 25.68 |
| Total retention | 4.30 |
| Retention/kg. | 0.095 |
| Intake/kg. | 0.665 |
| Urinary creatinine | 749 mg./24 hr. |
| Urinary creatine | 184 mg./24 hr. |

TABLE III

NITROGEN PARTITION IN THE URINE

| | DATA IN GM. N/24 HOUR | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| DATE | URINE VOL. | TOTAL | $NH_3$ + UREA | $NH_2$ ACID | URIC ACID | CREATININE | CREATINE | REST (BY DIFF.) |
| December, 1939 | | | | | | | | |
| 17 | 1200 | 23.50 | 22.11 | 0.213 | 0.137 | 0.302 | 0.101 | 0.64 |
| 18 | 1050 | 24.60 | 29.82 | 0.185 | 0.122 | 0.331 | 0.012 | 0.13 |
| 19 | 1050 | 22.60 | 21.03 | 0.472 | 0.123 | 0.327 | 0.042 | 0.61 |
| 20 | 4200* | 22.00 | 20.40 | – | 0.145 | 0.253 | 0.101 | 0.10 |
| 21 | 1200 | 20.80 | 19.59 | 0.324 | 0.144 | 0.245 | 0.101 | 0.40 |
| Av. | | 22.70 | 20.79 | 6.299 | 0.134 | 0.292 | 0.071 | |

*Diuretic given was mercupurin. The patient was given a high protein diet, and though he suffered gastrointestinal upsets, it was thought that his daily protein intake was about 50 to 75 Gm./day. He weighed 121 pounds at time of first observation.

Liver function tests were carried out during this period of time. Cholesterol partition showed the total cholesterol to be 170 mg., free cholesterol, 39.8 mg., and cholesterol esters, 130.2 mg. for each 100 c.c. of blood. The ratio of cholesterol esters to free cholesterol would then be 3:1, a normal figure. The blood prothrombin was found to be 73 per cent of normal. The galactose tolerance showed 1.056 Gm. of galactose excreted in the four-hour urine specimen following administration of 40

Gm. of the sugar. Bromsulphonphthalein test showed slight retention of the dye in a two-hour period. Since possibly a proteolytic enzyme was present and was causing excess breakdown of the plasma protein, a portion of serum from the patient was mixed with an equal amount of serum from a patient with normal level of plasma proteins and the determination of the total protein carried out before and after incubation of the mixture for a forty-eight-hour period. There was no appreciable change in the protein concentration.

The patient was readmitted on Jan. 27, 1940, with the history that in the previous three weeks diarrhea and vomiting had been present and for the most part at night. The stools had been thin in consistency, small in amount, and clay-colored. He had experienced some discomfort on defecation due to the hemorrhoids. About the same time he had developed redness over the face. The redness spread down to the arms and was patchy in distribution. This had persisted on the upper extremities but had cleared up on the face. Itching of the areas had been moderate. Swelling in the lower extremities had for the most part receded. Potassium nitrate in large doses had not been effective in controlling the abdominal effusion. He had received a number of intravenous injections of mercupurin with little success in reducing the edema.

Some physical changes had occurred. The legs were slender; no pitting was present. However, the abdomen was still markedly distended, but liver and spleen were definitely smaller. There was a slight redness over the cheeks and nose, but an angry-appearing area was present on each arm. About some areas there was a definite border, but in others a faded appearance was present. The skin was very dry, and its temperature was not increased. The veins on the forehead were quite prominent, but cutaneous wasting was of extreme degree. There was evidence of marked pulmonary hypostasis. Cardiac tones were distant. The blood pressure was systolic 110, and diastolic 65 mm. of mercury.

Laboratory data showed little change. The hemoglobin was 13.5 Gm. per 100 c.c. of blood by the Haden-Hauser method; the leucocyte count was 14,950; and the erythrocyte count was 4.83 million for each cubic millimeter of blood. The differential showed 97 polymorphonuclear cells, one eosinophile, and two endothelial cells. The serum calcium was found to be very low, 4.8 mg.; serum phosphorus, 3.5 mg.; and serum phosphatase, 40.7 units for each 100 c.c. of blood. The serum calcium several days later was found to be 5.6 mg. for each 100 c.c. of blood. The serum sodium was 287 mg.; nonprotein nitrogen, 40 mg.; total protein, 4.4 Gm.; serum albumin, 1.6 Gm.; serum globulin, 2.3 Gm.; and fibrinogen, 0.5 Gm. for each 100 c.c. of blood. The serum cholesterol was found to be 153 mg.; icterus index, 10 units; carbon dioxide combining power, 48 volumes for each 100 c.c. of blood. The basal metabolic rate was –24 per cent of normal. The electrocardiograph showed no conduction disturbance but extremely low voltage interpreted as indicative of advanced myocardial disease.

The patient was desperately ill. Because of the lack of systemic reaction and local heat accompanying the redness, the skin infection was regarded as erysipeloid rather than a true erysipelas. While no bleeding had occurred, his blood prothrombin level was found to be 40 per cent of normal. Vitamin K and bile salt therapy resulted in elevation of the prothrombin level to 71 per cent in a period of 12 days. The patient progressively lost strength; there was no appreciable increase in plasma proteins though desperate means were undertaken by use of intravenous therapy. Lyophile serum was used in rather large quantities, but blood samples withdrawn immediately following administration of the material showed no appreciable elevation of the serum proteins. The appetite was lost to a large extent, and though

the patient imbibed moderate amounts of milk and water, the dryness of the skin persisted, and finally the skin reaction present on admission disappeared.

On March 6 he developed marked pulmonary oppression. Abdominal paracentesis and heavy dosage of mercurial diuretics failed to relieve the progressive pulmonary edema. Showers of moist râles could be heard throughout the chest, and the cardiac tones became inaudible. Bilateral external strabismus occurred. Death occurred the next day and was caused by circulatory collapse.

*Post Mortem.*—The body was that of a fairly well-developed, poorly nourished, adolescent white male measuring 146 cm. in length. There was present moderate generalized edema. The amount of fat over the chest and the abdomen was negligible. The peritoneal cavity contained 500 c.c. of clear, straw-colored, serous fluid. The diaphragm was at the level of the fourth rib on each side. No mesenteric lymphadenopathy was present. One adhesion which was rather firm and fibrous was noted between the right and left lobes of the liver.

The left pleural cavity contained 1,600 c.c. of fluid while 1,400 c.c. were removed from the right side. The visceral and parietal pleurae were smooth and shining, and at the base of the left lung the pleura was thickened and grayish in color. No mediastinal shift was present, and the pericardial space was obliterated by dense fibrous adhesions. The heart weighed 150 Gm., and both auricles were moderately dilated. The myocardium measured 1 cm. in thickness in the left ventricle and 0.2 cm. in the right ventricle. The right lung weighed 350 Gm.; the left lung, 400 Gm. Both were fairly small, reddish in color, and only partly crepitant. The bronchi contained a moderate amount of clear, frothy mucoid material. On cut section a moderate amount of clear and frothy, bloody material could be scraped away.

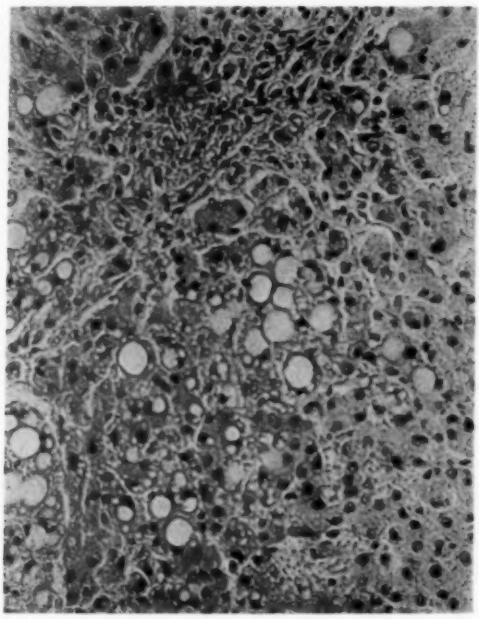

Fig. 1.—Photomicrograph of liver substance of patient with Pick's syndrome, showing the amount of destruction and fibrosis.

The spleen weighed 250 Gm. The surface was smooth, and the capsule grossly did not appear markedly thickened. The organ was dark purplish blue in color.

No evidence of esophageal varices was present. A small ulcer about 1 cm. in diameter was found in the first portion of the duodenum. The liver weighed 1,400 Gm. and presented a fine nodular appearance. The organ showed some capsular thickening and increased resistance to cutting. The kidneys, bladder, and the gall bladder appeared essentially normal. The bone marrow from the femur showed some fatty change.

The microscopic changes were essentially as follows. The muscle fibers of the heart were small. The nuclei were prominent, and scattered throughout were a moderate number of lymphocytes. Many areas showed moderate increase in connective tissue especially in the perivascular spaces. The pericardium was thickened, dense, and hyaline-like. The outermost portion contained a large number of lymphocytes and a few eosinophiles. Also a moderate amount of fibrosis of the myocardium was present.

Fig. 2.—Photomicrograph of spleen, showing perisplenitis.

The lungs showed changes which were for the most part hypostatic. A large number of the alveoli were filled with secretion, heart failure cells, red blood cells, lymphocytes, and acute inflammatory cells. The alveolar walls were edematous, the vessels were congested, and in areas the architecture of the lung was partly obscured. The mucosa of the bronchi was ulcerated in part, and the lumen was filled with acute inflammatory cells. The pleura at the base of the left lung showed marked thickening, was hyaline-like in appearance, and contained a moderate number of chronic inflammatory cells. In many areas the dense connective tissue extended down into the pulmonary tissue, and many vessels were surrounded by a thick layer of dense connective tissue.

The capsule of the spleen was thickened and contained many chronic inflammatory cells. The mucosa in one area of the duodenum was completely destroyed, and an ulcer niche extended down to the musculature. The borders were undermined and the

surface was covered with thin layers of fibrin. Section of the ileum showed some thickening of serosal layer which was infiltrated also with chronic inflammatory cells.

The liver showed marked autolysis. A number of liver cells were destroyed, and there was increased fibrous tissue about the portal spaces and the periphery of the lobules though in some areas the architecture was fairly well preserved. In some areas the central vein was dilated and had a surrounding zone of congestion and fibrosis. In other areas the architecture of the lobules was not so well maintained, and these were surrounded by scattered areas of fibrosis showing regenerating cells. The capsule was thickened, and all of the fibrous tissue showed round-cell infiltration. Bile duct proliferation was present but not marked. No bile stasis was noted. The serosal layer of the gall bladder was markedly thickened, contained many new blood vessels, and showed evidence of chronic inflammation. The adrenals were surrounded by a thick layer of dense connective tissue and contained chronic inflammatory cells.

Fig. 3.—Photomicrograph of heart, showing the myocardial degenerative and inflammatory changes.

## DISCUSSION

Pick's syndrome[1] has been said to result most frequently from pericarditis due to tuberculosis, rheumatic fever, or pneumococcal infection though at times the pathogenesis is so obscure as to defy definite classification. Infection within the serous-lined membranes brings about adhesions between mediastinal structures, especially the heart and its surrounding pericardial sac. As the pericardium becomes thickened, there is compression of the myocardium as well as of the great veins related to the mediastinum (constrictive heart disease). Embarrassment to the contractions of the heart results and is most apt to be severe during the

diastolic phase of the cardiac cycle. With a decrease in the size of the cardiac chambers there is a compensatory increase in the cardiac rate giving rise to the rapid small pulse so frequently described.

Congestion of the liver occurs as a result of pressure on the hepatic veins and gives rise to the hepatic pseudocirrhosis. The effusion into the serous-lined spaces is brought about by the constriction of venous return to the heart. With increase in amount of free fluid there is added pressure on great vessels, with more and more edema.

The syndrome of pseudocirrhosis may manifest itself by symptoms of cardiac failure, or by a purely insidious onset, though at times abdominal signs may quite early suggest the condition in its most typical onset which constitutes the true disease. When edema occurs it is by far the most striking feature noted. Signs which may be found include high venous pressure, narrowed pulse pressure due to both lowered systolic pressure and elevated diastolic pressure, systolic retraction of areas of the thoracic cage, especially in the left axillary region, pleural effusion, weak or distant cardiac tones, and marked hepatosplenomegaly. Electrocardiographic evidence may assist in the diagnosis by revealing inverted T waves and low voltage in the absence of axial deviation. Roentgenologic evidence of mediastinal fixation may possibly be demonstrated, but calcium deposits in the pericardial sac are not often to be found.

Kelly[2] reviewed the literature from 1846 until 1902 and collected thirty-nine cases. Sixteen of the group were younger than 20 years of age. He quoted Ensminger in saying that the condition was due not to connective tissue proliferation in the liver but to different causes. Emphasis was placed by him upon interference with circulation of the inferior vena cava. A second school of thought held that the ascites was due to peritonitis, and a third group held that the disease was based upon the two factors. Kelly noted that nine of the thirty-nine cases had unilateral or bilateral pleural effusion.

While it cannot be denied that a systemic infection in these cases has found localization in the serous-lined spaces of the body, nor that part of the picture is due to stasis of cardiac oppression, it would appear quite logical that the hypoproteinemia is an important factor in the production of the edematous state.

Suppression of the plasma proteins may be due to nutritional disturbances, to loss of protein in the urine, ascitic fluid, or the tissues because of increased capillary permeability, or to defective protein formation.

While our patient suffered frequent gastrointestinal upsets, apparently because of decreased gastric capacity and duodenal ulcer, his daily protein intake was approximately 50-75 Gm. His ability to retain nitrogen and the finding of normal nitrogen partition in the urine with a high protein intake would speak for effective absorption and the utiliza-

tion of amino acids. When the nitrogen intake was high, the retention was also high. He was able to catabolize proteins normally as shown in Table III. A nutritional disturbance could not have been the major factor in this case. Further evidence against nutritional origin of the hypoproteinemia is the finding of Wangensteen and collaborators[3] in their study of patients with malignant tumors and protein deficiencies, on a basis of lowered intake. Such subjects were able to utilize the protein of human or bovine plasma introduced into the circulation. In one case the drop in urinary nitrogen following introduction of intravenous protein they felt indicated storage of the material—no significant rise in the blood nonprotein nitrogen having occurred. The relationship between the total nonprotein nitrogen and urea of both blood and urine of this patient showed no appreciable alteration of normal catabolism of protein. That protein introduced intravenously can be utilized by the body would strengthen the belief, in view of the fact that it was true in our case also, that no profound nutritional disturbance was the basis for the depression of plasma protein. It has been shown that the amount of protein introduced into the parenteral system alone about quadrupled the amount lost in the ascitic fluid. Considering the disproportion involved, it hardly seems likely that removal of the ascitic fluid could have exerted more than a very minor part in the production of the hypoproteinemia.

Our patient lost no appreciable amount of protein in the urine. An attempt to demonstrate presence of proteolytic enzymes in the blood failed, as the mixture of a specimen of the patient's plasma with an equal amount of plasma containing normal protein level showed no appreciable change in protein concentration before and after incubation for forty-eight hours.

We are forced to return for an explanation of the hypoproteinemia to suppression of plasma protein formation as a consequence of hepatic disease. The backing up of a column of blood to the liver from the heart occasions an amount of hepatic damage which is irreparable in that one vital function, which was for the most part destroyed. The child was unable to elaborate plasma albumin. The rate of formation of other plasma proteins appeared to be normal. Other hepatic function tests such as the galactose tolerance test, cholesterol partition, and bromsulphonphthalein test were normal, and it was only comparatively late in the course of the disease that the marked increase in concentration of serum phosphatase in the plasma and the depression of the prothrombin gave indication that other activities were being placed in jeopardy.

It has been frequently noted in clinical hepatitis that fibrinogen depression in the blood parallels the degree of hepatic damage. The last fibrinogen determination of the plasma of our patient proved to be normal. Production of an Eck fistula in the experimental animal is followed by slowed process of plasma protein formation when plasma pro-

tein depletion has first been produced by plasmapheresis (Knutti). Warner, Brinkhous, and Smith[4] have spoken of reduction of plasma prothrombin as related to hepatic injury, which indicates hepatic origin of some of the plasma globulins. However, in our patient, the plasma prothombin returned to a fairly high level (73 per cent of normal) following the administration of vitamin K and bile salts, and the globulin fraction of the plasma proteins was maintained within normal limits.

A marked depression in serum calcium accompanied the depression of the blood proteins. With the very low level of serum calcium, the patient at no time manifested any sign of tetany; this indicated that the serum calcium was largely in the ionized form and the decrease was almost entirely in the calcium bound to protein. The fact that the carbon dioxide combining power of the blood was slightly toward the acid side may have also been a factor which prevented tetany. However, it is conceivable that other factors were also active. Hypocalcemia is a common accompaniment of hypoproteinemia, but the degree of lowering noted in this patient is not often observed.

The disturbance in serum albumin level brought about by pseudocirrhosis of the liver is comparable if not identical with the entity described as idiopathic hypoproteinemia including generalized edema without demonstrable cause since at necropsy there were found in such patients minimal hepatic changes described as interstitial hepatitis. Binger and Keith[5] in their discussion of edema of indeterminate origin raised the question as to the possible loss on the part of the individual of the ability to form serum proteins from the absorbed amino acids.

Thompson, McQuarrie, and Bell[6] in their interesting case of atrophic cirrhosis of the liver spoke of the low level of plasma proteins as not being influenced by high protein feeding though a strongly positive nitrogen balance was maintained for longer than six months. These investigators concluded from their studies that the edema resulting from this type of disease differed in no way from that due to hypoproteinemia of starvation or excessive protein loss, and that hypoproteinemia in absence of albuminuria or protein starvation should be regarded as presumptive evidence of hepatic failure. The data from the patient reported here quite support this view. It is to be emphasized that in this patient formation of serum albumin was markedly affected while other functions of the liver were maintained at close to normal levels. Thus it appears that the formation of serum albumin is one function of the liver most likely to be damaged by chronic passive congestion of this organ.

## CONCLUSIONS

We have studied a case of Pick's syndrome with special reference to the hepatic function which may have been involved by the pseudocirrhotic changes. The damage to the liver was quite selective; even short-

ly before the death of the patient there was scant evidence to indicate general hepatic insufficiency. Standing out strikingly in the case was the failure of the body to regenerate plasma proteins, particularly the albumin fraction. Apparently no protein was lost through the kidney. The child was able to retain nitrogen when the dietary protein was sufficiently high, and the amounts of protein lost through paracentesis were far less than the amounts administered in transfusions, yet all efforts to increase the level of plasma albumin were unsuccessful. Other functions of the liver seemed to remain approximately normal so far as they could be judged by the various tests of hepatic function. As the liver and the spleen seemed to be the only organs involved which might be concerned in protein formation, these observations are considered as further evidence to indicate that elaboration of albumin is a function of the liver. It would appear that the cells of the liver having to do with the function of albumin formation are particularly susceptible to the effects of passive congestion in that organ.

The writers wish to express their appreciation to Dr. Genevieve Stearns for her valuable criticisms and suggestions. We are indebted also to the Department of Pathology for the use of their records and data.

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# CALCIFICATION OF THE ARTERIES OF AN INFANT

## Report of a Case

Archie H. Baggenstoss, M.D., and Haddow M. Keith, M.D.,
Rochester, Minn.

INSTANCES of extensive calcification of the arteries of infants are rare. The first report on this condition in the literature was probably that of Durante[1] in 1899. In addition to his report, we have been able to collect reports of eight more cases. Anderson and Schlesinger[2] reported another case at the meeting of the Society for Pediatric Research in May, 1940, but their report has not yet been published. We have summarized the data from the reported cases in Table I and in addition are reporting one case of our own.

### REPORT OF CASE

A baby girl, aged eight weeks, was admitted to the hospital on April 9, 1939. The patient was a full-term baby, and delivery had been normal. The mother had been well during pregnancy, and the puerperium had been uneventful. The baby's feedings had consisted of a mixture containing evaporated milk and later a mixture of one part condensed milk and four parts water. She had not been given any cod liver oil. The child's birth weight was 8 pounds (3.6 kg.). She gained weight well and weighed 9 pounds 6 ounces (4.3 kg.) at five weeks of age. The first symptom was vomiting which began at 9:00 P.M. on April 8, the day before admission. During the night the child cried much more than usual; the abdomen was distended with gas; and there were considerable belching and vomiting. The child had been having normal stools, however.

Examination at the hospital revealed that the baby was extremely dehydrated. The fontanel was soft. The tongue was thickly coated, and the extremities were cold and clammy. External heat was applied at once. Forty cubic centimeters of blood was given intramuscularly and 5 per cent solution of glucose subcutaneously. Four hours after admission the baby died suddenly.

*Necropsy.*—The body measured 58 cm. in length and was estimated to weigh 15 pounds (6.8 kg.). When the peritoneal cavity was opened, the liver was found to extend 5.5 cm. below the xiphoid process and 4 cm. below the costal margin in the right midclavicular line. Each pleural cavity contained 10 c.c. of clear fluid. The transverse diameter of the pericardium was 7 cm., and the pericardial sac contained 15 c.c. of blood-tinged fluid. The thymus weighed about 15 gm. and appeared normal.

The heart weighed 42 gm. (normal 23 gm.) and was reddish brown. The myocardium was of a less firm consistency than normal. There was hemorrhage into the wall of the right auricle, and some hemorrhagic spots appeared on the anterior surface of the left ventricle. The cut surface of the myocardium was reddish brown. The foramen ovale was closed. Dilatation of the left ventricle was graded 3 (Fig. 1). The endocardium of the left ventricle was mottled, and there were scattered irregular grayish yellow patches on the reddish brown surface. The papillary muscles were markedly flattened. At the apex of the left ventricle the

From the Sections on Pathologic Anatomy and Pediatrics, The Mayo Clinic.

TABLE I

CASES OF CALCIFICATION OF ARTERIES IN INFANTS REPORTED IN THE LITERATURE

| AUTHOR | AGE AND SEX | ARTERIES INVOLVED | LOCATION AND APPEARANCE OF LESIONS | OTHER ANATOMIC DIAGNOSES | AUTHOR'S INTERPRETATION OF CALCIFICATION |
|---|---|---|---|---|---|
| Durante | 7 months' gestation (?) | Pulmonary and to a lesser degree the aorta | Inner media, the site of fatty degeneration and calcification; intima involved in places | Navel infection; general peritonitis | Congenital |
| Bryant and White | 6 months M. | Peripheral and visceral arteries of medium size | Extensive degeneration and calcification of inner 5/6 of media; intima enormously thickened | Phimosis; hydronephrosis; gangrene of toes | Syphilis with hydronephrosis and "chronic fibroid changes in the kidneys" responsible |
| Jaffe | 2 days M. | Pulmonary artery | Necrosis and calcification of inner half of the media | Tentorial tear with hemorrhage at base of brain; atelectasis of lungs; edema and ascites | Severe hydramnion in mother responsible |
| Surbek | 3 days F. | Large and medium-sized arteries | Calcification of inner portion of media with extension into the intima; calcium surrounded by granulation tissue and giant cells. Adventitia thickened by fibrous tissue and inflammatory cells | Chronic nephritis; pericarditis; splenomegaly | Chronic nephritis and resulting "calcium gout" responsible |
| Verocay | 5¾ months F. | Coronary artery and arteries of abdominal organs | Calcification of media and thickening of intima | Congenital syphilis | Congenital syphilis |
| Johansson | 3 months M. | Peripheral arteries of extremities | Degeneration and calcification of intima and media | Osteogenesis imperfecta | None |
| Forrer | 3 months M. | Medium-sized arteries and inferior vena cava | Media transformed into ring of calcium; calcium clumps surrounded by granulation tissue and giant cells; intima greatly thickened; plasma cells, lymphocytes and leucocytes in adventitia | Mild chronic glomerulonephritis; splenomegaly; granuloma of navel | Sepsis with resulting injury to arterial wall plus disturbance in calcium metabolism |
| Iff | 8 months' gestation M. | Larger and medium-sized arteries, umbilical arteries | Calcification of inner media but occasionally entire media; occasionally also intima and adventitia; lymphocytes and leucocytes around calcium deposits and focal collections of lymphocytes in adventitia | Atelectasis of lungs; edema of skin; ascites; hemorrhages | Incomplete development of ground substance of arteries; hydramnion responsible (?) |
| Lightwood | 2¼ years F. | Medium-sized and small arteries | Media, the seat of widespread destruction and massive calcification; proliferation of subintimal connective tissue; slight thickening of adventitia | Chronic kidney disease; renal insufficiency; bronchopneumonia | Lime water feedings and phasic disorder of calcium and phosphorus metabolism |

myocardial wall was greatly thinned and appeared fibrotic. The right ventricle appeared to be slightly dilated but otherwise normal. The valves appeared to be

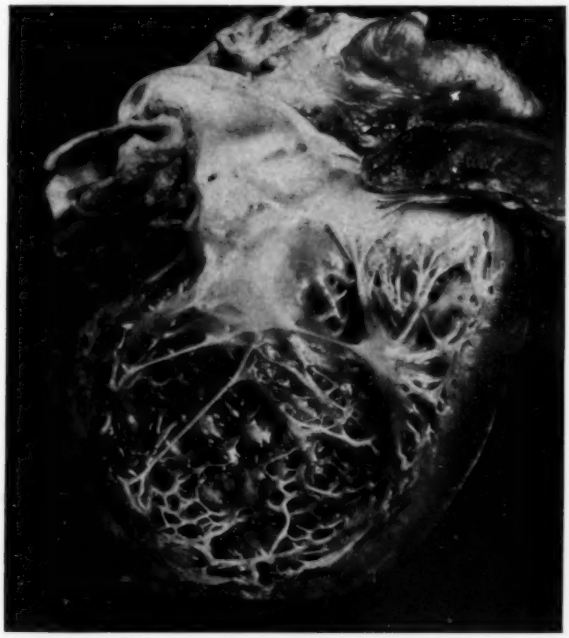

Fig. 1.—Dilatation of the left ventricle with chronic infarction of the myocardium.

Fig. 2.—Thickening of coronary arteries. The lumen was greatly narrowed.

normal. The coronary arteries were somewhat tortuous silver streaks of abnormal thickness (Fig. 2). On cross section the walls were found to be greatly thickened,

and the lumen was narrowed greatly (Fig. 3a). Sclerosis was graded 3+; no thrombi were found. The lungs appeared normal except for edema, grade 1. The other organs appeared normal on gross examination.

*Histologic Examination.*—In sections of both coronary arteries and their branches striking calcification and distortion of the media were encountered (Fig. 3a). The continuity of the inner layers of the media was disrupted by numerous deposits of calcium throughout. In the neighborhood of these deposits proliferation of the fibroblasts was pronounced, and occasional giant cells were seen. The outer layer of the media was thin, and the muscle and elastic fibers were fragmented. The intima was greatly thickened by fibroblastic proliferation, and consequent narrowing of the lumen had occurred. The only noteworthy changes in the adventitia were the presence of small focal collections of lymphocytes and eosinophilic polymorphonuclear leucocytes.

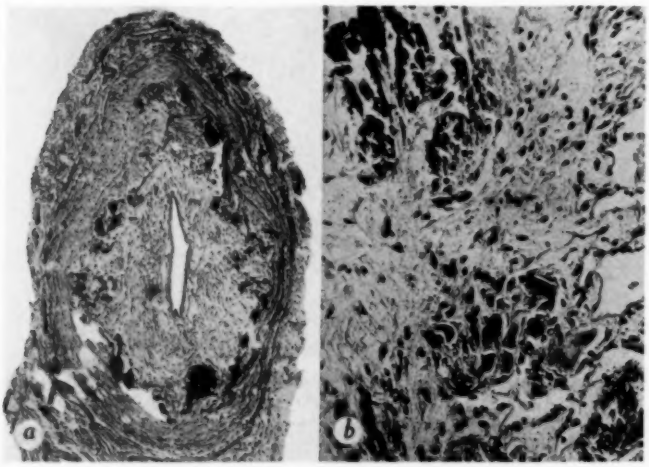


Fig. 3.—Calcification; *a*, of inner media of the right coronary artery with foreign body reaction and tremendous thickening of intima by fibrous connective tissue (hematoxylin and eosin, ×50); *b*, of the myocardium. Deposits of calcium and fibrosis may be noted (hematoxylin and eosin ×210).

In sections of the left ventricle and interventricular septum, there were focal areas of necrosis of muscle fibers with hemorrhage and evidence of replacement by fibrous connective tissue. In some of these areas deposits of calcium salts were surrounded by fibroblasts and giant cells (Fig. 3*b*). In some regions the calcium appeared as fine, bluish, dustlike deposits, but elsewhere larger masses were present. In the muscle fibers adjacent to these deposits there were numerous lipoid droplets. The endocardium of the left ventricle was greatly thickened by the marked proliferation of loose connective tissue.

In the ascending aorta and pulmonary artery there were scattered areas of calcification of the internal elastic lamina as well as patches of calcification in the elastic fibers adjacent to the adventitia.

Lesions similar to those found in the coronary arteries were present in the small arteries of the mesentery, the kidneys, and the periadrenal connective tissue (Fig. 4). The deposits of calcium stained blue with hematoxylin and eosin and black with Kossa's stain. In the kidneys the arteriolar walls were thickened, and the lumina in some instances were obliterated almost entirely. In addition to these vascular changes, there was a slight increase in the number of endothelial cells

lining the glomerular capillaries, and in a few instances hyalinization of a portion of, or of the entire, tuft had occurred. Deposits of calcium were present in many of the glomeruli. The epithelial cells in many of the convoluted tubules were swollen and vacuolated. Hyaline granular degeneration was occasionally present in these cells.

Fig. 4.—Periadrenal artery with changes similar to those seen in the coronary artery (hematoxylin and eosin, ×160).

In sections of both lungs severe edema of the septa of the connective tissue was noted. In these septa of connective tissue the fibers were separated by a moderate amount of edema fluid, and there were a number of large mononuclear cells with basophilic cytoplasm. There was no evidence of the so-called fibrinoid swelling of the collagen, however. The connective tissue about the bronchi and vessels was somewhat increased in amount.

In the spleen the reticular cells in the centers of many of the Malpighian bodies were undergoing degenerative changes, and the sinuses of the pulp were congested. There was a moderate increase in the fat content of the cells of the liver, but no other abnormality was noted. Sections of the other organs were not remarkable.

The anatomic diagnoses were calcification of coronary, mesenteric, renal, and periadrenal arteries, chronic infarction of the myocardium, cardiac hypertrophy with dilatation, grade 3, of the left ventricle, focal calcification of heart and kidneys, edema of lungs, fatty changes in the liver, emaciation, and dehydration, grade 2.

## PATHOGENESIS

In an analysis of the cases reported in the literature, the following facts appear to be significant: 1. The patients were all very young. This fact makes it quite possible that the arterial lesions were present before birth. In other words, these are probably instances of congenital calcification of the arteries. 2. Infection was present in four of the cases (congenital syphilis in one). 3. Renal disease was described in four cases. 4. The inner portion of the media was the site of predilection

for the deposition of calcium in these cases. 5. In four of the cases reported in the literature and in our own, deposits of calcium were present in various organs as well as in the blood vessels.

In an analysis of the pathogenesis of the arterial lesions, two general types of calcification must be considered, namely, (1) calcification secondary to primary injury of the blood vessel (so-called dystrophic calcification), and (2) calcification as a result of changes in the blood so that all its calcium cannot be retained in solution (disturbances of calcium metabolism with metastatic calcification).

In the dystrophic type of calcification, the primary injury may be the result of an infection, that is, syphilis or sepsis, as was true in several of the cases reported in the literature. Another disease that should be considered, regardless of whether or not it is considered a specific type of infection, is periarteritis nodosa. In our case the collections of lymphocytes and eosinophiles in the adventitia and the proliferation of the intimal connective tissue tend to support this diagnosis. Necrosis of the media has been considered the primary lesion in periarteritis nodosa by many pathologists, and there can consequently be no theoretic objection to interpreting the histologic picture in our case as that of healed periarteritis nodosa with partial calcification of a previously necrotic media. Against the idea that we are dealing with a case of healed periarteritis nodosa is the fact that, as far as we are aware, calcification has never been described in the reported cases of healed periarteritis nodosa. In the various cases reported[3-7] the process of healing has always been described as one of formation of scar tissue. The fact also that deposits of calcium occurred in the aorta, heart, and kidneys would be difficult to explain on the basis of a diagnosis of periarteritis nodosa. Furthermore, to support such a diagnosis it would almost have to be assumed that the infection of the arteries was actually present before birth, and this would indeed seem unlikely.

Another form of dystrophic calcification, according to Iff,[8] may occur as a result of incomplete development of the so-called ground substance of the arteries. This ground substance has also been called chromotropic, mucoid, or interstitial substance.[9] Hueck[10] stated that it is the precursor of collagen and elastic connective tissue and exists in adult life as a reserve for the replacement of collagenous and elastic tissue. According to Björling,[11] it is a form of connective tissue to be distinguished from collagenous and elastic tissue particularly by its metachromasia when stained by Unna's polychrome methylene blue. It then stains more or less red, whereas collagen and elastic fibers stain blue. According to Schultz,[9] this substance has a special affinity for lipoids and calcium probably because of its high content of chondroitin-sulfuric acid. Ssolowjew[12] found that it is most abundant in the inner sheaths of the media in arteries of the elastic type.

In our case, as well as in most of the cases reported in the literature[1, 8, 13-18] (Table I), the inner portion of the media is the site of calci-

fication. Consequently it seems plausible to assume that certain inherent characteristics of this portion of the arterial wall make this a site of predilection for calcification. In our case there was no histologic evidence of incomplete development or of injury to this portion of the arterial wall, aside from the calcification.

The conditions which may result in disturbances of calcium metabolism with so-called metastatic calcification remain to be considered. The fact that in four of the cases previously reported, as well as in our own, there were deposits of calcium in various organs aside from those in the blood vessels indicates that these conditions deserve serious consideration. Widespread deposits of calcium throughout the body have been found in diseases of bone (osteomyelitis, myelogenous leucemia, neoplastic disease, osteogenesis imperfecta), advanced disease of the kidneys with renal insufficiency (that is, renal rickets), hyperfunctioning parathyroid glands, parathyroid adenomas, and hypervitaminosis D.

There was no grossly demonstrable evidence of any disease of the bone in our case, but it is interesting to note that Johansson[17] reported a case of osteogenesis imperfecta with widespread arterial calcification. There was likewise no evidence of severe renal disease in our case. In the literature, however, renal disease was reported in four cases (Table I), and in three of these it was severe.[13, 15, 19] Cases of renal rickets accompanied by arterial calcification in children have been reported by Smyth and Goldman[20] and Shelling and Remsen.[21] In a review of nephrosclerosis in childhood, Mitchell,[22] in 1930, found that in twenty-two of the eighty cases in which there were sufficient notes on the postmortem examination, the statement was made that the aorta or other blood vessels were thickened, sclerotic, or contained atheromatous patches. When calcification occurs in such instances, it is generally attributed to retention of phosphates in the blood with consequent depression of the calcium content and its deposition in the tissues. Hyperfunction of the parathyroid glands presumably follows and also plays an important role. We were unable to rule out completely the possibility that a hyperfunctioning parathyroid gland or an adenoma may have been responsible for the disease in our case since, unfortunately, neither the parathyroid glands nor the bones were examined histologically. Metastatic calcification, including severe calcification of the arteries, has been observed in human beings suffering from von Recklinghausen's disease[23, 24] and has been produced in animals by injecting parathyroid extract (parathormone).[25, 26] Nevertheless, it appears extremely unlikely that osteitis fibrosa cystica of a degree severe enough to result in metastatic calcification could occur in an infant of this age.

Although there are no facts in the history to support it, from a theoretic standpoint the possibility that we were dealing with the accidental overdosage of vitamin D from which a disturbance in calcium metabolism and consequent metastatic calcification resulted must be considered seriously. Instances of overdosage of vitamin D among children

which led to deposition of calcium in the kidneys have been reported by Putschar[27] and Thatcher.[28] Similar cases of calcification of the arteries have been described by Eisler[29] and Thomasen.[30] Calcification by overdosage with vitamin D has been produced experimentally in as short a time as four days by Laas[31] and, according to Ham,[32] as quickly as forty-eight hours after the injection of a single massive dose of vitamin D. Consequently the age of this infant need not necessarily rule out the possibility of overdosage of vitamin D. Because of the rapidity with which calcification may occur, we cannot be certain that our case is one of congenital calcification.

## SUMMARY AND CONCLUSIONS

Extensive calcification of the arteries and deposits of calcium in the heart and kidneys of an infant aged 8 weeks have been described. The calcium was deposited chiefly in the inner half of the media and was particularly prominent in the arteries of the heart, mesentery, periadrenal tissue, and kidneys. The calcification of the media was accompanied by a marked intimal proliferation.

The cause of the calcification is unknown, but the most likely possibilities are (1) an abnormality in the arterial wall and other tissues as a result of either infection or incomplete development, (2) a severe disturbance in calcium metabolism, such as might be produced by overdosage of vitamin D, and (3) a combination of the first two possibilities.

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# RENAL RICKETS

PETER G. DANIS, M.D., AND JULIUS A. ROSSEN, M.D.
ST. LOUIS, MO.

RENAL dwarfism, renal infantilism, or renal rickets, as it is commonly designated, is a syndrome rather than a specific disease of infancy and childhood. Since the extensive study and thorough review of the literature by Mitchell,[1] the condition has been more frequently reported in American literature. Despite all these reports, the exact underlying pathologic and physiologic connections between the various parts of the syndrome are not sufficiently understood. No hypothesis completely explains the entire condition. At least ninety cases of renal rickets have been reported, the average age of the patient being 7 years when diagnosed.

*Etiology.*—The exact etiology is unknown, although various factors apparently produce the condition. In our cases, there is a history of chicken pox preceding the onset of symptoms, but it is hard to conceive that, with such a vague, insidious, and slow developing type of nephritis, varicella alone would be sufficient etiology. We recognize an hereditary familial tendency toward kidney disease. This has been frequently reported in regard to kidney diseases and appears to be a possible factor in our cases, as the children are brother and sister.

Mitchell[2] has offered the hypothesis that renal retention of phosphates results in the high excretion of phosphates into the intestinal tract where they combine with the calcium, preventing calcium absorption and thereby producing a depletion of calcium of the bones. The state of chronic acidosis resulting from the renal damage puts a great demand on the body for fixed base, thereby removing calcium from the bones, especially when the ammonia mineral formation is reduced as a result of kidney damage. The exact resulting mechanism, therefore, is the mobilization of the calcium and other minerals, thereby depleting the bones. However, we find cases where the rickets is mild and heals during the course of the disease.

Specifically associated with metabolism, Chown[3] has suggested endocrine factors as causative, particularly the pituitary. Today we have come to recognize a definite growth factor in the secretion of the pituitary gland and that the pituitary gland exerts a definite action on the rest of the glands of internal secretion. Therefore, pituitary function indirectly would always be associated where one is dealing with dwarfism; however, there is no evidence to justify the consideration that the disease is primarily of pituitary origin. Gross[4] and Albright and associates[5] have demonstrated in experiment the close relationship

From the Department of Pediatrics, St. Louis University School of Medicine, and the St. Mary's Group of Hospitals.

of calcium and phosphorus metabolism to the parathyroid glands. Pappenheimer and Wilens[6] have called attention to the autopsy evidence of parathyroid hyperplasia in prolonged renal insufficiency. The presence in some cases of pathologic fractures and roentgenologic appearance of the bone simulating that seen in parathyroid osteogenic disturbances point toward the parathyroid as an etiological factor in this syndrome. The theory has been offered by Smyth and Goldman[7] that there is disturbance in parathyroid control, resulting in dwarfism due to Thompson's antigrowth factor of the parathyroid; that this is associated with parathyroid hypertrophy which is a result of a hyperphosphotemia; that the parathyroid secretion attempted to reduce the blood phosphorus which has not been normally secreted by the kidney; and that this results in a depletion secondarily of the bone calcium; in other words, that the hyperphosphotemia rather than the blood calcium metabolism is the primary factor. This, however, may be entirely secondary to the disturbed metabolism resulting from kidney disease.

The theory that the parathyroid gland is the primary seat of difficulty, or what might be called the parathyroid theory proper, is based on the finding of parathyroid hyperplasia and hypoplasia at autopsy; that the hypersecretion of the parathyroid interfering with calcium and phosphorus metabolism produces a deposit of calcium and fibrosis of the kidney. The kidney condition thereby becomes secondary. The repeated findings of definite congenital anomalies of the urinary tract in so considerable a number of reported patients with this condition makes this theory seem to us rather remote. In one of the cases reported below, there is definite fluorographic evidence of congenital dilatation of the ureters which would tend to bear this out.

CASE 1.—N. T. (Fig. 1) was aged 1 year and 10 months, weighed 15 pounds and 12 ounces, and was 70 cm. tall. He was brought to St. Louis University Clinic because of failure to gain weight, abnormal thirst, food cravings, and severe loss of appetite over a period of about five months following a moderate attack of chicken pox. The child presented such a marked picture of malnutrition, fragility, and weakness that he was admitted to the hospital on Oct. 21, 1933, where the following history was obtained.

N. T. was born a full-term, 6¾-pound male, following a simple, uncomplicated delivery. No cyanosis, convulsions, nor abnormalities were noted at birth. He nursed well at the breast until 1 year of age.

At 8 months of age patient began on one egg a day and cream of wheat, but did not receive cod-liver oil until 1 year and 3 months of age, at which time it was not retained and was discontinued after the second dose. At 1 year he weighed 20 pounds. He had no illness until he was 14 months old, and his color was good until that time; he has had no immunizing vaccines. The child began teething at 7 months and has his lower and upper incisors now. At 7 months he sat up. He speaks in sentences now. During life there has been no intercurrent illness or complaint other than chronic constipation. The father and mother are well, and the mother's diet during pregnancy was satisfactory. There are four older siblings—an 8-year-old girl, a 7-year-old boy, a 5-year-old girl, and a 3-year-old girl, all in good health. The patient is the fifth child. The children have no skin diseases. The family circumstances were those of an upper class clinic type family of foreign descent, with average intelligence.

The physical examination was negative except for evidence of rickets and malnutrition. The head was large with prominent frontal bones, open anterior fontanel, and dry scalp with veins that were unduly prominent.

The gums were spongy, and the tonsils large. The chest was cone-shaped, with a moderate degree of costochondral enlargement. The abdomen was large and distended "potbelly type." His skin was thin, pale, and had a yellowish tinge to it. The upper extremities had a poorly developed musculature and prominent distal ends of both radial and ulnar bones. Lower extremities were bowed, and the distal ends of the tibia and fibula were very prominent.

Fig. 1.—N. T., Case 1.

*Routine laboratory findings* showed red blood cells, 2,800,000, and white blood cells, 14,500. The Schilling differential showed myelocytes, 0; immature forms, 1 per cent; stabs, 2 per cent; segmenters, 70 per cent; lymphocytes, 24 per cent; monocytes, 1 per cent; eosinophiles, 0. Hemoglobin (Dare) was 70 per cent; blood pressure, 80/60; nonprotein nitrogen, 32 per cent; blood calcium, 8.4 mg.; phosphorus, 6.1 mg.; blood chlorides, 460 mg.; serum protein, 9.6. Blood Wassermann and Kahn tests were negative.

Urinalysis showed: 2+ sugar; 2+ acetone; a trace of albumin; granular and hyaline casts, 2 to 3 per high power field; 6 to 10 white blood cells per high power field; 2 to 3 red blood cells per high power field. The specimen was centrifuged before examination. The Mosenthal test revealed specific gravity to be 1.002 to 1.006 throughout day and night.

Intravenous skiodan showed no kidney shadows on three occasions. The phenolsulphonphthalein test total was 14 per cent function.

X-ray of the long bones showed healing rickets with irregularity of diaphysis, with many so-called phosphorus lines present. (Fig. 2.) The skull plate was normal.

With the above information, the first suspicion was that the child had a diabetes or a renal glycosuria associated with nephritis which, in some way, was related to

malnutrition and was associated with rickets. In an attempt to correlate the entire picture, the diagnosis of renal rickets was considered. Further study (Table I and Chart I) convinced us that this was the condition; however, the child had a sister (Case 2) who at this time presented the same general picture without sufficient evidence on blood study or detailed physical examination to make a definite diagnosis. N. T. was observed in the hospital over a period of months, but the condition remained at a standstill, regardless of improved nutrition. No

Fig. 2.—Examination of the lower extremities revealed marked knock-kneed deformity from bowing of the lower end of the femurs. There is enlargement of the ends of all the bones, with irregularity of the epiphyseal lines, indicative of ricketic involvement.

particular therapy was used, except in combating the anemia, because of the reported evidence that various treatments were valueless. The child went home on Dec. 22, 1933, only to return on December 30, with physical findings of tetany. At this time the hospital admission states: "Child following a good meal, having been fairly well since leaving hospital, vomited and body became stiff." He was rushed to the hospital. Examination revealed the same pale, small child, with stiff arms and legs held in partial extension and the thumb tightly clasped in the hand. A diagnosis of tetany was made. At this time the blood calcium was 8.6 and blood phosphorus was 6.6 mg. On administration of calcium gluconate, the child improved. Table II gives further laboratory findings.

On July 16, 1934, the child re-entered the hospital because of a cough. Admission weight was 20½ pounds. Shortly after entrance, a diagnosis of whooping cough was made, and the child was sent to St. Louis Isolation Hospital where he made an uneventful recovery.

On July 29, 1935, he entered because of sudden illness, with rapid respiration. The diagnosis was upper respiratory infection. The patient was in a coma. During his stay the progress of renal rickets was studied again. Tables I and II show the blood chemistry. Phenolsulphonphthalein output was only 5 per cent, and nonprotein nitrogen, 65 per cent, demonstrating progressive kidney deficiency.

TABLE I

SUGAR TOLERANCE TESTS IN CASE 1

| | TEST 1 10/25/33 | TEST 2 11/20/33 | TEST 3 7/29/35 |
|---|---|---|---|
| Fasting specimen | 143 mg. | 100 mg. | 96 mg. |
| 1-hour examination | 222 | 211 | 190 |
| 2-hour examination | 167 | 164 | 160 |
| 4-hour examination | 126 | 111 | 110 |

On Nov. 11, 1935, the child re-entered the hospital for general study. The nonprotein nitrogen was still above normal, and the phenolsulphonphthalein test showed 20 per cent efficiency. The sugar tolerance curve, however, was more normal, fasting sugar being 80 mg.; first hour, 131 mg.; second hour, 118 mg.; third hour, 98 mg. per 100 c.c. of blood.

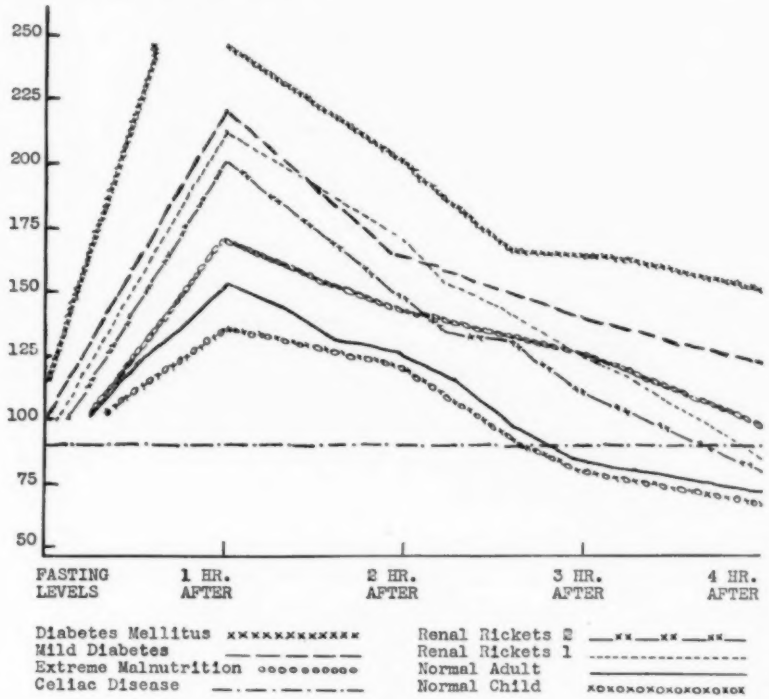


Chart I.—Sugar tolerance in health and disease.

On Feb. 24, 1936, the child again re-entered the hospital. This time, however, he was acutely ill. Physical examination still revealed a markedly emaciated child with an acute nasopharyngitis. On Feb. 26, 1936, he developed a severe laryngitis with marked edema of the glottis and died on March 1. During this period the constant seriousness of the child's condition prevented extensive blood chemistry study. Nonprotein nitrogen was 60.

An autopsy was performed by members of the Pathology Department of St. Louis University, the pertinent details of which follow.

TABLE II

SPECIAL LABORATORY STUDIES (N. T., CASE 1)

| DATE | P.S.P. | N.P.N. | CALCIUM | PHOSPHORUS | UREA NITROGEN | CREATININE | SERUM PROTEIN | ALBUMIN | GLOBULIN | CHLORIDE | B.P. | CHOLESTEROL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1933: | | | | | | | | | | | | |
| 10/26 | 14% | 32 | 8.1 | 6.1 | 12.9 | 84 | 9.6 | | | 460 | 90/70 | |
| 10/30 | 15.5 | | 7.8 | | | | | | | | | |
| 11/8 | | 33 | | | | | | | | | 95/54 | |
| 11/26 | 20 | 25 | 8.19 | | | | | | | | | |
| 12/28 | | | 8.67 | | | | | | | | | |
| 12/30 | | 32 | 7.6 | 6.6 | | | 10.1 | | | | | |
| 1934: | | | | | | | | | | | | |
| 1/26 | 36 | | 8.6 | 6.1 | | | | | | | | |
| 2/3 | | 55 | | | | | | | | | | |
| 7/29 | 5 | 65 | | | | | | | | | | |
| 1935: | | | | | | | | | | | | |
| 2/21 | | 60 | 9.1 | 6.7 | | | | | | 458 | | |
| 2/24 | | 55 | 8.1 | 4.9 | | | 8.1 | 3.9 | 4 | 418 | 85/35 | 126 |
| 2/28 | 20% | 60 | | | | | | | | | | |

N.B. All numbers not otherwise indicated are given in milligrams per 100 c.c. of blood.

The body was that of a poorly developed, malnourished, white boy who appeared about 1 year of age, although he actually was 5 years old. The skin was pale and sallow throughout except for the post-mortem lividity in the dorsal and dependent positions. At the corners of the mouth were a few excoriations. All the skeletal muscles were soft and pliable, resembling putty. The scalp was covered by an abundance of wavy hair of fine texture. Both the frontal and parietal bones exhibited bossing. No abnormality was encountered in the eyes, nose, or face. All the teeth seemed in normal condition. In the midline was a recent tracheotomy wound, which appeared quite clean. There were no gross deformities in the chest wall.

Both femora bowed laterally, while the tibiae described an anterior, as well as a slight lateral, curvature and were slightly enlarged at their distal ends. Each knee joint was more prominent than usual. The bones were shorter than average for age.

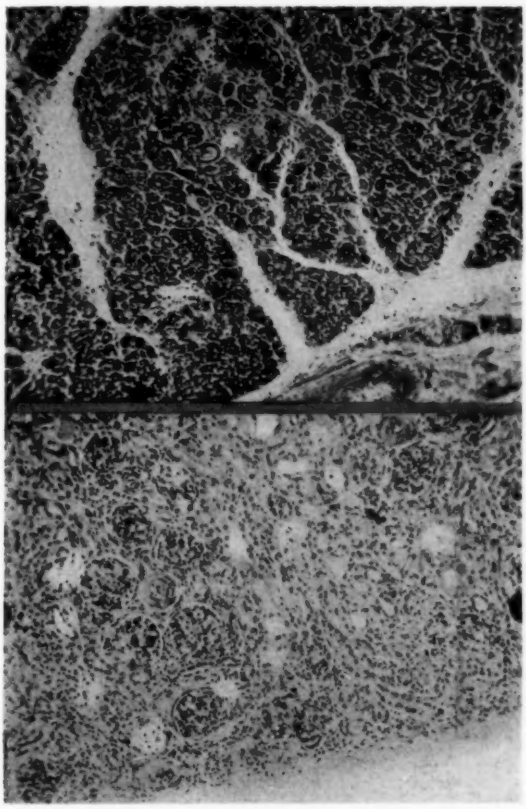

Fig. 3.

Fig. 4.

Fig. 3.—Photomicrograph showing the slight pancreatic scarring.
Fig. 4.—Photomicrograph showing the medial thickening of two arterioles.

The epiglottis was swollen and soft, and its surface was covered by gray, friable, necrotic material.

The liver was of the usual size with a thin capsule covering a slightly softer, brownish-red parenchyma. Some slight smoothing out of the anterior inferior

border was present. On cut surface the usual liver markings were found, although the color was somewhat more grayish than usual.

Most of the medullae of the adrenals were degenerated; only a narrow rim of soft, grayish tissue remained. The cortices consisted of thin, even, ochre yellow capsules. Each kidney was considerably reduced in size, of a pale color, and had an irregular surface. Some fetal lobular markings were present. The capsules stripped with difficulty and revealed finely granular, pale surfaces. No cysts were found. The cut surface of each showed a marked thinning of the cortex and an irregular indistinct corticomedullary boundary. The medullae were of a grayish-brown color and slightly reduced in amount. A moderate increase in the

Fig. 5.

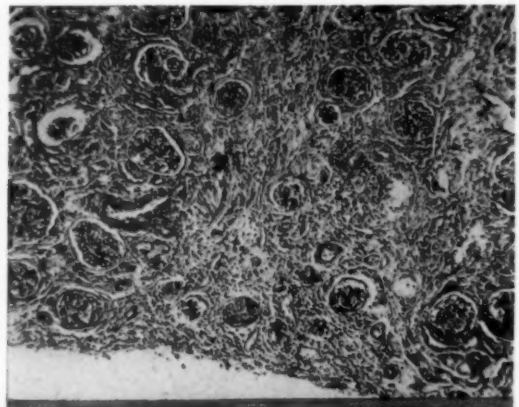

Fig. 6.

Fig. 5.—Photomicrograph showing the distortion of renal parenchyma by fibrous tissue, fibrous thickening of the glomerular capsules, and some adhesions between the capillary loops and the capsule of some of the glomeruli.

Fig. 6.—Photomicrograph demonstrating the irregular costochondral junction and the formation of an island of bony tissue.

peripelvic fat was found. There was no dilatation of the pelves and their walls were thin and shiny throughout. The distal third of each ureter was mildly dilated, but no vesicular dilatation was encountered and no demonstrable obstruction of the distal portion of the urinary tract was encountered. A thin intact mucosa lined the small bladder, and the tiny prostate was firm.

Microscopic examination of the epiglottis revealed an edema of all the structure, with considerable hyperemia. Neutrophiles were present throughout in large numbers. Considerable necrosis was found, and in places the surface epithelium was denuded, exposing an area covered by debris, fibrin, neutrophiles, and some gram-positive cocci grouped in irregular clusters.

The histologic architecture of the pancreas was slightly changed in many lobules by a very slight fibrosis (Fig. 3). All the parenchymatous cells appeared normal. One of the medium-sized arteries exhibited a slight medial thickening. Considerable reticular hyperplasia was evidenced in the spleen by its dense appearance as well as by the formation of many blood channels.

Hyalinization of about 8 per cent of the glomeruli was present in the sections from the kidneys. Many of the glomerular capsules were thickened with fibrous connective tissue, and some adhesions to the glomerular capillary tufts were seen. The medium-sized arterioles showed a moderate fibrosis of their medial coats (Fig. 4). There was considerable variation in the size of the convoluted tubules and many hyaline casts were seen. The tubular epithelium was swollen, pale, and vacuolated. Throughout the parenchyma considerable fibrosis, with many lymphocytes and some monocytes, was in evidence (Fig. 5).

The costochondral zone was quite irregular and the cartilage did not possess the usual orderly lacunar arrangement (Fig. 6). Some fibrosis of the marrow was present in many locations.

Fig. 7.—M. T., Case 2.

Case 2.—M. T. (Fig. 7), aged 3 years, weighing 18 pounds and 14 ounces, and 74 cm. tall, entered the hospital on Nov. 3, 1933, following the diagnosis of renal rickets on her brother. She was too short for her age and was underweight. She had peculiar food cravings and a polyuria.

Fig. 8.—Both kidneys seemed to be extremely small, but neither showed evidence of opaque stone. Opaque ureteral catheters extend well into both kidney pelves. Injection of opaque material reveals normal pyelograms, but there is marked dilatation of the ureters.

Fig. 9.—Examination of the long bones of the lower extremities revealed transverse fractures of the proximal and middle thirds of the right fibula, without displacement of the fragment and with little, if any, new bone formation.

She had been breast fed for the first year of life and during that time had enjoyed excellent health. During the second summer of life she had a chronic diarrhea and, before completely recovered, had developed chicken pox. Her developmental history was normal, and she had no complaints.

Her family history was essentially negative except for the history of a brother who had been just previously hospitalized and whose case had been diagnosed as renal rickets.

Physical examination revealed an undersize, underweight child whose skin had a yellow pale tint to it that was too marked to be associated merely with her light complexion and hair. There was slight beading of the ribs at the costochondral junction and a marked pot belly, associated with poor general muscular tone. There was a marked genu valgum, and the forehead was rather prominent. Other than these signs of dwarfism and rickets, the physical findings were those of a normal child.

*Routine laboratory examinations* showed red blood count 3,900,000; white blood count, 9,000; hemoglobin, 70 per cent; blood pressure 90/70; Wassermann and Kahn tests, negative; nonprotein nitrogen, 31 mg.; calcium, 8.9 mg.; phosphorus, 4.5 mg.; chlorides, 450 mg.; serum protein, 6.7 mg.; albumin, 5.5 mg.; globulin, 1.2 mg.

Urinalysis was negative except for granular casts, 1+ sugar, and a trace of albumin. Mosenthal tests revealed persistently low specific gravity of from 1.001 to 1.006; the phenolsulphonphthalein test showed 10 per cent function.

X-ray pictures of the long bones were negative except for slight haziness of diaphysis. Findings in the skull were negative. X-ray of wrist revealed two centers of ossification, indicating slight retardation of growth for age.

Cystoscopic examination revealed both ureter and kidney pelves dilated (Fig. 8).

With the above information and the history of disease in her brother, the child was considered to have an early mild form of the disease and was discharged.

*Progress Notes.*—The child returned on July 11, 1934, because of loss of appetite and weight. At this time, she weighed 19 pounds and 12 ounces, and was 4 years of age. X-rays of the wrist joints again showed only two centers of ossification. She now had definite thirst polyuria and nocturia. Results of blood studies are shown in Table IV. The phenolsulphonphthalein had dropped to 10 per cent, but nonprotein nitrogen was only 34 per cent. The child proved to be developing whooping cough and was discharged from the hospital.

On Nov. 11, 1935, the child re-entered the hospital, without complaints, for further study. Height was 80 cm. and weight 28 pounds. She had a marked anemia. Table IV gives results of other studies.

On Feb. 6, 1939, the child re-entered the hospital as an emergency case with acute tetany, a blood calcium of 6.9 mg., and a blood phosphorus of 5.2. She weighed 24½ pounds and was 86 cm. tall. Her mental development as judged at this time was greatly ahead of her physical growth. She was 8 years old and in the third grade at school. There was no appreciable edema, although the typical lemon pale appearance was still present as on previous admissions. Blood chlorides were found to be 550 mg.; icteric index, 10; the van den Bergh test, negative; blood pressure, 78/40. The Mosenthal concentration test was as before, with no evidence of concentration and with variations from 0.04 to 0.06. The red blood count was 1,970,000; the white blood count, 12,000; and hemoglobin, 32 per cent. Further laboratory studies are reported in Tables III and IV.

X-rays now revealed a definite pathologic fracture in the region of the proximal one-third of the fibula, with marked irregularities over the diaphysis in the region of all the joints (Fig. 9).

After a blood transfusion and intravenous administration of calcium, the tetany was relieved. However, it recurred in mild form every two or three days despite elevated blood calcium. During the time associated with marked attacks of

TABLE III

SUGAR TOLERANCE TESTS IN CASE 2

| | TEST 1 7/11/34 | TEST 2 11/11/35 | TEST 3 2/14/39 |
|---|---|---|---|
| Fasting specimen | 95 mg. | 87 mg. | 82 mg. |
| 1-hour examination | 250 | 200 | 182 |
| 2-hour examination | 286 | 140 | 160 |
| 3-hour examination | 200 | 90 | 125 |
| 4-hour examination | 154 | 71 | 70 |

rapid breathing, the child's carbon dioxide tension varied from a mild compensated alkalosis to a severe acidosis. A second blood transfusion, however, arrested this, and the child went home.

At about this time an article by Goldmann and Ekstein[8] appeared, recounting the presence of acidosis in renal rickets and its relation to the imbalancing of bases present. The theory put forth was to the effect that there was too high a sodium reserve in comparison with potassium. It was suggested that a high potassium-low sodium diet might benefit this.

On April 17, 1939, the child was brought back to the hospital. Laboratory data (Table IV) were obtained, and the child was put on a high potassium diet consisting mainly of potatoes and bananas and little meat.

On Aug. 14, 1939, the child re-entered and laboratory data were obtained. During the interim she had had no attacks of tetany or rapid breathing, and remained on special diet satisfactorily.

On Oct. 24, 1939, however, she re-entered with the history of recent recurring attacks, but of a much milder form. Blood counts again revealed a severe anemia which was treated by transfusion and iron by mouth. The child was sent home and did not have to return during the next eight months.

## DIFFERENTIAL DIAGNOSIS

From the appearance of both these children it was suggested at first that they were purely cases of marked malnutrition following starvation. The starvation we believed to be precipitated by an acute infection, namely chicken pox. However, this was a rather severe picture to be presented as the result of chicken pox. From the history and roentgenologic examination, scurvy was ruled out. Rickets was found by x-ray of the long bones, other x-ray pictures, the blood findings, and the calcium-phosphorus ratio. Sugar being present in the urine, diabetes, renal glycosuria, pentosuria, and alimentary glycosuria had to be considered. Pentosuria was ruled out by chemical urinalysis; renal glycosuria, by the sugar tolerance tests. Alimentary glycosuria was excluded by a fasting blood sugar determination and urinalysis. Diabetes in severe form was ruled out by the sugar tolerance test. However, the sugar tolerance curve did resemble that of mild diabetes. It is of special interest to note here that later examinations of the pancreas revealed fibrous replacement. We had thus in Case 1 the picture of rickets, retardation of growth, and mild diabetes, associated with evidence of chronic kidney disease. The chronic kidney disease was based on phenolsulphonphthalein values, the low specific gravity, and the Mosenthal test. These latter findings, of course, were brought out

TABLE IV

SPECIAL LABORATORY STUDIES (M. T., CASE 2)

| DATE | P.S.P. | N.P.N. | CALCIUM | PHOSPHORUS | SERUM PROTEIN | ALBUMIN | GLOBULIN | CHLORIDE | B.P. | CHOLESTEROL |
|---|---|---|---|---|---|---|---|---|---|---|
| 11/ 3/33 | 30% | 30 | 8.9 | 3.5 | | | | | 90/60 | |
| 7/13/34 | 10% | 30 | 8.5 | 3.6 | | | | 470 | | |
| 11/11/35 | 5% | 40 | 9.4 | 4.6 | 8.1 | 4.6 | 3.5 | | 90/50 | 103 |
| 2/ 9/39 | 5% | 50 | 6.9 | 5.2 | 11.4 | 8.8 | 2.6 | 550 | | |
| 2/15/39 | | | 8.8 | 4.9 | 6.7 | 5 | 1 | | | 169 |
| 2/26/39 | | | 9.2 | 4.3 | | | | | | |
| 4/11/39 | | 50 | 9.7 | 6.1 | | | | 488 | | |
| 6/17/39 | | | 9.4 | 5.4 | | | | | | |
| 8/14/39 | 10% | 55 | 8.6 | 4.8 | 8 | 6.1 | 3.7 | 532 | | |
| 10/24/39 | | 85 | 8.9 | 3.2 | 5.8 | 4.6 | 1.2 | 504 | | 375 |
| 11/ 4/39 | 10% | 70 | 9.2 | 4.1 | 5.6 | 4.3 | 1.2 | 492 | | 315 |

The cholesterol readings for this method of determination normally average from 160 to 180 mg.
All numbers not otherwise indicated are given in milligrams per 100 c.c. of blood.

after the other possible diagnoses were excluded. Mitchell had called attention to the presence of a sugar tolerance curve in renal rickets which resembled that of mild diabetes, although for some unknown reason, case reports in the literature have completely ignored this factor; in some instances where very extensive study had been made, a blood sugar test was not even listed. With these findings, the diagnosis of renal rickets was made. The course of both these children since first examination has obviously proved the diagnosis.

## DISCUSSION

Several factors are worth remention. The children were brother and sister, indicating a possible hereditary familial factor in the etiology. They were at an age when there is difficulty in deciding whether or not rickets is pure infantile rickets. N. T. (Case 1) was previously presented before the St. Louis Pediatric Society, and at that time it was considered that the high diabetes-like sugar tolerance curve might possibly be the result of the inability to handle carbohydrates as a result of starvation. Since, with the improved nutrition, this particular finding had become less marked, this explanation would appear logical. This high sugar tolerance curve has been previously reported with renal rickets, but has been given little consideration by most authors. A point of special interest is that, with the diet so low in vitamins B, C, and D, one would expect frequent upper respiratory infections to accompany the course in these children. However, from the history and hospital observation, we note they were exceptionally free from colds. The outstanding feature in the course from the standpoint of treatment has been the clinical response to a high potassium diet. Since the child has been following such a diet, hospitalization has not been necessary, attacks of tetany have ceased, and anemia has not progressed as rapidly as during the previous two years. The simplicity of this dietary regime is offset only by the lack of clinical laboratory procedures practical and reliable enough to afford any accurate study of the actual biochemical changes resulting. This result, although interesting and important to the child, may therefore only be a clinical coincidental, and demands further use before definite opinions as to its value can be given.

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# ASTHMA COMPLICATED BY SUBCUTANEOUS EMPHYSEMA IN CHILDREN

## Report of Case

H. H. Skinner, M.D.
Yakima, Wash.

THE rarity of this condition is emphasized by the paucity of literature to be studied. Van Fleet, Miller, and Scott, of Los Angeles, after a painstaking search, were able to unearth but fifteen cases of subcutaneous emphysema accompanying asthma, in ten adults and five children. To these they added four more cases, in two of which the patients were 5 and 10 years of age, respectively.

In the consideration of only those children of 10 years or under, of which there are but seven cases recorded, several interesting aspects present themselves.

Kahn's patient, a girl 8 years of age, had paroxysms of asthma for six years, although the attacks were not particularly violent. She had infiltration in her upper chest, back, over both shoulders, neck, and both sides of the lower half of the face. It was of so marked a degree that she presented the appearance of infectious parotitis. Crepitation was present. There was no great amount of pain. It took ten days to absorb the air. Since air ordinarily is absorbed much more quickly, there must have been a continuance of the process of infiltration.

Dietrich reported a five-year-old girl who had experienced other asthma attacks. During this particular seizure, she vomited and retched almost incessantly for twenty-four hours before dyspnea began. Crepitation was felt over her neck and shoulders and in the axillae, and subclavicular regions. By the sixth day all air had been absorbed.

Dietrich's second case was that of a boy 7½ years of age. His other asthmatic attacks had occurred with increasing severity. During this particular incursion, he developed severe pain under the left scapula. Two days later an extensive subcutaneous emphysema was discovered in the neck, axillae, and upper thorax. X-ray films showed much mediastinal air, all of which disappeared within a week.

Van Fleet, Miller and Scott's first case was that of a girl 10 years old. She had asthma and dyspnea, and complained of soreness in her throat. The swelling of her right neck was so complete that it obliterated all bony landmarks from the angle of her jaw to below the clavicle. How long this continued is not stated. Recovery was complete.

Their second patient was a boy of 5 years, who had had repeated attacks of asthma. When first seen, he had been suffering for twenty-four

hours. Respirations were 65, and temperature 101.6° F. The emphysema extended from the neck down into the abdomen on the right side, extending to the right hip. In nine days all was absorbed.

All of these children had had previous attacks, Kahn's over a period of six of her eight years of life; Dietrich's 7½-year-old male patient had attacks of increasing severity before the emphysema appeared; his 5-year-old female patient immediately preceded hers with unusually severe vomiting and retching. I have no data on the cases of Davidson of Great Britain or Pastorino of Uruguay. Van Fleet, Miller, and Scott's two patients and my one did not experience inordinate paroxysms before swelling and crepitation appeared. Although a marked elevation in temperature may be observed at the onset, it is not necessarily an accompaniment. When present, it soon subsides and seems to have no relation to the longevity of the swelling.

Pain may or may not precede and be a part of the condition. However, there is the sensitiveness and tenderness one would expect with air under the skin. Crepitation is always felt. Visible swelling is not observed over all areas involved. It is usually quite marked over the area from the neck to the clavicles. The neck is always infiltrated, the process usually extending onto the shoulders and into the axillae.

C. J. L. was born March 27, 1932, in Seattle, Wash., and her family moved to Tacoma five months later. A younger brother was born there. Both children had normal births. They came from Tacoma to Yakima Nov. 4, 1939.

When asthma appeared first about three years ago, the child was cared for by Dr. D. M. Dayton, of Tacoma. There had been no history of asthma in the family, although the mother has hay fever; other pollens also have troubled her to a certain degree. C. J. L. has never had hay fever, but has been quite sensitive to smoke, especially coal smoke.

The patient had always been subject to colds, "one right after another all her life." She had influenza and asthma first in the winter of 1938 and 1939. A sanipractor was the family health advisor. Her mother states that her attacks were characterized by coughing, wheezing, and vomiting, but there had been no temperature before this present experience during the last of February, 1940. Five years ago she had a hard siege of pertussis, which began in July and continued through the summer.

C. J. L. was first seen Feb. 29, 1940, at 11:30 P.M., because of vomiting and wheezing. Temperature was 98° F. (rectal). Physical examination revealed no especial pathology of throat, ears, or teeth; there were 1+ cervicals. The chest was rather flat, with squeaks, râles, and crackles audible all over it, both anteriorly and posteriorly. Respirations were distressed and noisy, with prolongation of the expiratory phase. The abdominal examination and reflexes were negative.

*Treatment.*—Six minims of adrenalin hypodermically did not relieve her condition, but morphine, 1/12 grain, and atropine, 1/300 grain, quieted her attack.

On March 1 at 9:45 A.M. she was comfortable, although typically asthmatic. Her temperature was 100.6° F. (rectal). Her mother called attention to an ovoid swelling extending from the throat 2 in. below the clavicle.

The blood picture was: hemoglobin, 70 per cent; red blood count, 4,310,000; white blood count, 16,000; polymorphonuclear cells, 83; small lymphocytes, 9; large lymphocytes, 4; transitionals, 4.

At 2:00 P.M. her temperature was still 100.6°. Crepitation was now felt over the entire left scapula area, extending into the left axilla and onto the chest. She complained of no pain, just a slight tenderness.

Fig. 1.—The lines mark the lower edges of the emphysema. The upper outlines on chest and shoulder were irregular and difficult to trace. The child's skin and the subcutaneous tissues were so invaded over the manubrium that they were markedly puffed up in the semilunar space. Over the left scapular area were many poorly defined, crackly spots.

On March 2 her temperature was normal. Chest sounds were improving, and the areas of crepitation extended onto the right side to the cleidomastoid muscle, as outlined in Fig. 1. The areas of crepitation were not continuous posteriorly. Rather, there were small islands where no crepitation could be described.

Her recovery was continuous and consistent. Although slight crepitation could be felt on March 7, it had completely disappeared three days later.

In studying the factors involved in the production of subcutaneous emphysema, one is misled by the preponderance of air in the tissues of the neck into the surmisal that air enters spaces under the skin from the apices of the lung or follows the large vascular trunks from the mediastinum into the neck. The anatomic arrangements of fascia render this route of entrance impossible.

Although the apices of the lungs rise one and one-half inches above the clavicles, they lie behind the subclavian vessels and the scaleni muscles, and the above structures are behind Colles' fascia. This tissue drops like a mantle from attachments in the upper neck to the clavicles and manubrium, effectively blocking off any air burrowing along the vessels from the mediastinum, as well as furnishing an effective barrier to the pleural sac of the lung tips. Only the external jugular pierces this fascia on its way to the deeper vein, and it is unlikely that the air follows along its sheath.

Then the air under the skin must come directly through the chest wall, probably from the lung into the mediastinum, through a break in the parietal pleura into the chest wall. As there are few reports of a pneumothorax being present, and my patient gave no such evidence, it is to be deduced that paroxysms of coughing did not rupture lung air cells into the pleural cavity but rather into the mediastinum, unless, and this is more likely, there was a point of adhesion between the visceral and parietal pleura. Thus, there would be established a direct communication between the lung and thoracic wall through which air would pass directly from alveoli to subcutaneous areas. It is apparently a continuous process for a few days since the extension of air under the skin is progressive and the supply of air is kept up despite the absorptive ability of the subcutaneous tissues.

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# INTEGRATION OF PSYCHIATRIC TEACHING WITH PEDIATRICS

ERIC KENT CLARKE, M.D., AND REYNOLD A. JENSEN, M.D.
MINNEAPOLIS, MINN.

DURING the past two decades great changes have been taking place in the teaching of psychiatry. These changes have followed the dynamic leadership of such men as Drs. Adolph Meyer, Macfie Campbell, C. B. Farrar, Edward Strecker, Douglas Singer, Franklin R. Ebaugh, and the medical directors of the National Committee for Mental Hygiene from Thomas W. Salmon, the first, through Dr. George S. Stevenson, the present director. These and many others have given direction to the trend psychiatric education has taken. Today, as a result of their labors, basic psychiatric principles are taught in every class A medical school in the country. The history of these changes is a fascinating chapter in the growth and development of medical school curricula.

The methods employed vary from school to school, but essentially they have many features in common. Active classroom work consisting of didactic lectures is reinforced by clerkships, outpatient clinic service, and interdepartmental consultation services, together with the examination of one or more patients as part of the clinical year's experience. There has been a gradual shift from the presentation of the standardized series of nosologic classifications to a consideration of the individual case with its intrinsic features. Along with this modification has come a shift in emphasis from the diagnostic to the dynamic concepts. In addition, we have noted less stress on the study of terminal conditions and more consideration of the early manifestations of maladjustments, with the aim of reclaiming the patient.

To date, most psychiatric instruction has dealt primarily with the adult and his adjustments to the everyday world. However, studies of the adult have brought out at least two significant facts worthy of accent: (1) the importance of the early formative years in the development of the personality and the molding of character traits which either aid and abet or hinder the individual in making a satisfactory adjustment later in life; and (2) a growing awareness of the significant role played by mental and emotional factors in the disease process. With few exceptions, the medical student today is not adequately exposed to these two important aspects of medical practice. Is not the time for another advance in enriching the medical curriculum at hand?

From the Psychiatric Clinic for Children, University of Minnesota Hospitals, Minneapolis.

Presented before the American Psychiatric Association, May, 1940, Cincinnati, Ohio.

Several factors have contributed to the slow development of this phase of medical education. One has been the attitude of the pediatrist, whose specialty is but 50 years old. Initially, his chief concern was the study, treatment, and prevention of the common childhood disorders which were claiming such a heavy toll among the young—the infectious diseases, malnutrition, lack of postnatal care, and the like. With the tremendous advances in the past fifty years, the pediatrist of today is able, in large measure, to protect the growing child from the ravages of illnesses feared a generation or so ago. He now has time to consider the more subtle factors involved in growth and development. His willingness to think along these new lines is reflected in a "Plan for Teaching of Mental Hygiene" recently published in THE JOURNAL OF PEDIATRICS (February, 1940) which emphatically stresses the necessity for general adoption of a basic program of instruction in the medical schools. Likewise, such books as *Babies Are Human Beings* by the Aldriches and *Let's Talk About Your Baby* by Tenney are indications of the interest the pediatrist is taking in problems of mental, emotional and social growth, as well as the problems arising out of management of that growth.

The field of child guidance is in its thirty-first year, the first clinic having been established in 1909 by Dr. William Healy. It was not until 1922 that the National Committee for Mental Hygiene, with the help of the Rockefeller and Commonwealth Funds, established the demonstration clinics.

Since that time there has been a phenomenal increase in the number of centers designed to study and treat behavior disorders of childhood. In 1909 there was one; in 1935 there were over 500 full- or part-time clinics rendering service to their respective communities. These clinics, however, have been peculiarly ignored by many members of the medical profession, and even today it is unusual to find many physicians alert to such services available in their community.

The explanation of this state of affairs is a matter of conjecture. It may lie in the fact that in the rapid growth and expansion of the child guidance program the clinic drifted away from medicine to take up a nearly independent existence among the social or educational agencies. This has led to the development of ideologies and terminologies which the average medical practitioner or pediatrist little understands, due in part to a lack of training in his own student days. The gap is further widened by distrust and suspicion based on this very lack of understanding so essential to acceptance.

The child guidance clinic is doing notable work, but it must be allowed that, despite its most aggressive efforts, the labors expended are only scratching the surface. There is an expressed need for a more intensive and extensive approach to the problem through the education of the medical student who, in his practice tomorrow, by his awareness of the

problems in the making, can do much in the matter of prevention. This, it is believed, can best be done by integrating psychiatric and pediatric teaching. Such a program is in process of definition at the University of Minnesota Medical School.

The University of Minnesota Medical School, we believe, has been progressive in its philosophy and emphasis. It was one of the first to establish a psychiatric service to the students attending the University. The Division of Adult Psychiatry has been strengthened materially during the past few years by the erection of a new, up-to-date psychiatric unit with provision for fifty-seven inpatients and an active outpatient service. A year and a half ago a psychiatric clinic for children was established to augment the program of adult psychiatry as well as that of pediatrics.

The clinic is a separate unit in the Medical School, operating on its own budget derived through the generosity of the Commonwealth Fund and the Stevens Avenue Home of Minneapolis. Its staff consists of two psychiatrists, three psychiatric social service workers, two psychologists, and an executive secretary, with the necessary secretarial assistants. A speech pathologist works in cooperation with the staff, as does a schoolteacher who is assigned to the pediatric wards of the hospital.

The desire from the beginning has been that, while the Psychiatric Clinic for Children be kept a separate administrative unit, the program should be developed as an integral part of the general educational program of the University. For this purpose, the psychiatrists have joint appointments in both the Department of Psychiatry and the Department of Pediatrics. The psychologists hold appointments in the Medical School and the Department of Psychology of the University, and the social service workers, in the School of Social Work, in addition to the Medical School.

Cases are referred to the clinic from the inpatient and outpatient pediatric services, including the specialized clinics such as diabetic, cardiac, and allergy, from outside physicians, from social agencies, both local and state, from schools, and from the juvenile courts. In addition to active case work, the clinic supplies a consultation service to the Department of Pediatrics.

Although the functions of the clinic are threefold—(1) rendering clinic service, (2) engaging in investigative work, and (3) medical teaching—only the latter will be considered because this paper is concerned with medical education.

The teaching aims of the clinic are simple and easily defined. In our program we endeavor:

1. To acquaint the student with the basic principles of emotional and mental growth, correlating these as far as possible with anatomic growth and development, stressing average development for the various age limits.

2. To stress the importance of infancy and childhood in their relationship to the environmental and social forces surrounding them in the molding of personality and character traits.

3. To acquaint the student with the importance of recognizing the social factors and to demonstrate the contribution of the psychiatric social worker in the study and treatment of sick, as well as emotionally disturbed, children.

4. To give the medical student a practical, as well as theoretical, understanding of the kinds of psychologic tests and other techniques, their evaluation and uses.

5. To introduce the student to as much case material as possible in order to: (a) stress the importance of emotional problems in relation to illness; (b) acquaint the student with basic methods of diagnosis and simple methods of psychiatric treatment; and (c) emphasize the necessity of treating a patient with an illness rather than the symptoms of an illness.

6. To introduce the student to the rapidly accumulating literature on psychosomatic medicine.

7. To prepare the student to recognize and accept responsibility in a preventive psychiatric program as he works with children and parents.

8. To acquaint him with resources available for the care and treatment of such problems with which he is unable to cope, in order that his clientele will not fall into the hands of incompetent and untrained persons.

An initial survey of teaching possibilities suggested an approach divided into two categories, direct and indirect.

In the direct approach our contact with the medical student begins in the third year. We are allotted six hours to present briefly the major behavior problems as they arise in infancy and early childhood, middle and late childhood, and the adolescent period. This series of lectures follows the presentation of several lectures devoted to a consideration of anatomic and psychologic growth and development. Following our series is a lecture on speech problems of children. During our series we aim to stress the importance of considering family patterns and familial attitudes in the production of emotional problems or faulty social adjustments. We also aim to stress prevention and suggest common-sense methods for dealing with such common problems as enuresis, feeding difficulties, and temper tantrums frequently encountered in medical practice.

In the senior year we have a twofold approach to the student. At our university the fourth-year medical student spends the entire year on his various clerkships. In addition to the pediatric clerkship, a regular lecture hour is set aside for pediatric clinical demonstrations. We are assigned three hours in this series. During the course of the

past year we had occasion to spend two of these hours discussing the psychogenic factors in bronchial asthma. Many students were thus introduced to the literature on this subject. During the third hour we arranged to have four children in the amphitheater, a newborn, a 4-month-old, a 7-month-old, and a 1-year-old infant, for presentation and a discussion of the rapidly shifting changes in this significant period of life. The interest in this presentation may be summed up in the comment of one student: "I'll never forget now that children are growing persons."

Our most intimate contact with fourth-year students is during that period spent on the clerkship in pediatrics. Twice weekly we hold staff conferences for consideration of our own cases. The pediatric clerks are required, as a part of their pediatric training, to sit in on these conferences. The sessions are conducted in the following manner: The problem for consideration is presented briefly and the source of referral mentioned. Often the case is one from the pediatric service which is assigned to one of the attending clerks. The social worker then supplies the social history, including backgrounds, etc. The psychologist reports the results of his investigations. The physical study, often including special laboratory work, is then presented, followed by the psychiatrist's review of his work with the case. From this point on, the student becomes an active participant in the conference. He is asked: What significant factors do you see in this situation? What other things would you want to know? How does this retarded child in the home influence the picture? Does the mother's extreme apprehension over this exigency mean anything? Of what importance was this severe illness of several years ago? What is your evaluation of the entire situation? What would you do if confronted with such a situation in private practice? What can we do in the treatment of the problem? These and similar queries serve to stimulate student participation in our conferences. Such a process allows for much direct teaching. References to literature, elaboration of simple mental mechanisms, mention of available community resources, clarification of misunderstandings of psychologic tests and their uses, etc., the techniques of approaching problems of family relationships—all are related to actual life situations. Out of these considerations grows a treatment plan. "Just what is psychiatric treatment?" is a question frequently asked by students as well as members of the resident staff. It is a question difficult to answer in the abstract, but it largely answers itself as the student begins to think about the modification of particular relationships in a given case. Psychiatric treatment becomes something real, rather than a vague generalization.

In our clinic we do not believe it a practical plan to permit the fourth-year student to do actual psychiatric work with children.

An attempt is made at the end of each conference hour to summarize briefly salient points worthy of consideration in general practice. Student participation in the conference has indicated a recognition of and an interest in mental and emotional factors as related to illness.

At the end of each clerkship period an examination in pediatrics is given in which psychiatric questions are included. The responses obtained have been gratifying. We have been pleased to note that several students have chosen as their topic for the final term paper required of all graduating seniors some phase of child psychiatry and medicine.

The resident pediatric staff likewise is drawn into the case conference. In addition, one hour a week is devoted to a seminar with the residents and interns on the pediatric service. During this hour psychiatric implications in pediatrics are scrutinized even more intensively. Also at this time the psychiatric social workers and psychologists have an opportunity to present their concepts and philosophy.

During the regular academic year the Department of Pediatrics conducts weekly seminars for its general staff. We are assigned responsibility for two of these seminars each quarter. Pertinent problems involving pediatrics and psychiatry are presented for consideration and discussion, and the literature is reviewed.

So much for the direct approaches through lectures, conferences, and seminars. A great deal of our most important work is done indirectly.

The psychiatric staff is represented on pediatric rounds with the expectation of being called upon to participate actively in the discussion at hand as it may relate to organic illness. Often we get in our most effective teaching on such occasions. In addition to the regular rounds, the psychiatric staff circulates freely through the children's wards. An attempt is made daily to see each child briefly, with the hope of becoming acquainted with the hospital population in order to render service where and when it is needed. The presence of the psychiatrist gives an opportunity for informal discussion of daily routine management of those children who present evidence of maladjustment or who seem unduly apprehensive or homesick. Brief talks with the resident medical staff, the medical clerks, the nursing staff, the teacher or occupational therapist serve to prevent standardized case work-up with a disregard for individual needs of the patient. The fact that the psychiatrist can use his stethoscope and ophthalmoscope and discuss laboratory reports with reasonable understanding has done much to win acceptance and to enhance teaching values.

The effort of the Psychiatric Clinic for Children is directed toward supplementing the more formal groundwork of psychiatric instruction given by the Division of Adult Psychiatry. Throughout all our contacts we try to place full emphasis on careful inquiry into every aspect of a child's life, rather than limiting the investigation to the immediate events leading up to hospitalization or referral to the clinic. Thus,

the habit of routine consideration of emotional factors is established, and an appreciation of the significance of seemingly trivial manifestations is created.

Obviously, we do not expect to turn out fully trained psychiatrists, for such training must come as postgraduate instruction. We will be content if we can build up in our students an attitude of willingness to consider and evaluate emotional and environmental factors as being on an equal basis with the x-ray report, the blood chemistry, and the temperature charts. If we can attain this objective, it will avoid much medical misadventure which, at present, unfortunately exists. In its place we will provide the means for a more effective medical practice in which the patient as a person cannot be denied consideration in treatment. In so doing we hope to inaugurate a program of prevention. Two years of experimentation in the integration of psychiatry into pediatric service have borne out expectations in the results of practical instruction. We feel it is important that the services be closely integrated, yet separately maintained.

# American Academy of Pediatrics

## Proceedings

### NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO—NOV. 16-18, 1939

### Round Table Discussion on Vitamin and Mineral Deficiencies

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| Chairman: | Dr. H. D. Kruse, New York, N. Y. |
| Assistants: | Dr. Allan M. Butler, Boston, Mass. |
| | Dr. George M. Guest, Cincinnati, Ohio |
| | Dr. Philip C. Jeans, Iowa City, Ia. |
| Secretaries: | Dr. Roy P. Forbes, Denver, Colo. |
| | Dr. Urban J. Busiek, Springfield, Mo. |

CHAIRMAN KRUSE.—Only a part of this broad subject, vitamin and mineral deficiencies, can be covered in a limited time; hence, it has been decided to focus the discussion on the detection of deficiency diseases by the newer methods and on the related consideration, the concept of the latent state.

In modern medicine, detection of disease has come to play a new and increasing part. It differs from diagnosis. Diagnosis is the determination of the distinctive nature of a case of disease. In the past it was mainly the sick who consulted a physician and usually they came with signs or symptoms which attested to their sickness. The physician's task was to ascertain the nature of their malady. Then came the trend to early diagnosis. Patients with complaints presented themselves so early that it became necessary to elucidate the earliest signs and symptoms. Since patients came so early that signs or symptoms were indistinct and since the complaints were both real and fancied, the physician had this new task which preceded diagnosis, namely, detection of disease. Thus, the physician now had two responsibilities: first, to determine whether disease is present; and second, if it is present, its nature.

As in diagnosing, the physician's tools in detecting disease are clinical methods. These depend on signs and symptoms. Use of these is linked with the philosophy which has permeated medicine, whether in diagnosis or detection, that disease is morphologic in the sense that it produces lesions. In pathology and medicine, much effort has been spent on correlating lesions with signs and symptoms. In this, the microscope, serving another purpose besides a close-up of a macroscopic lesion, has been used to detect the earliest histologic changes, lesions so small as to be invisible to the naked eye. Yet the recognition of microscopic lesions as distinct from gross lesions has been a tacit acknowledgment that disease has stages. It is becoming more generally recognized that neither health nor disease is a homogeneous state, and that the transition from health to gross morphologic changes is not one step. From perfect health to advanced disease is a gradient, with health merging almost imperceptibly into disease. Moreover, early deviations from health are often manifested in dysfunctions, long before morphologic changes appear; these

dysfunctions are reflected in signs and symptoms. Functional disorders, so often dismissed in the past, may have significance as initial stages of disease. That does not mean that changes in bodily materials have not occurred, but they are below clinical perceptibility, even microscopic, and often are not of a character adapted to microscopic examination. Physiologic and chemical methods are needed.

Even before perceptible dysfunction, changes may be occurring in the body which are not manifest. For ascertaining the status of the earliest deviation, these physiologic and chemical methods are likewise needed. Clinical signs based on lesions may be late; by the time morphologic changes set in, the disease is well on its way. Even those manifest signs and symptoms indicating functional without gross morphologic disturbance do not give the first clues to deviation from health. To be sure, clinical signs, for their particular purpose, are and always will be no less useful. In the sick, they are essential tools of diagnosing the disease and gauging severity. But to meet the new purpose, appraisement of bodily status and detection of earliest deviations from health, new methods, more sensitive, are needed.

Nowhere is this situation better exemplified than in deficiency diseases. Not the least important outcome, from the standpoint of diagnosis and treatment, has been consequent clarification of specific signs and symptoms of each deficiency disease. Even more important for early diagnosis was the study of the pathogenesis of each disease, particularly the sequence of signs and the earliest sign. Hence, today most deficiency diseases can be detected clinically at the first appearance of discernible signs. But before the first signs of the manifest stage, deficiency diseases in their earliest form exist in the latent state. It is interesting that in studies on tetany, the latent state was originally recognized and described more than three decades ago; then it passed through a period of relative neglect, largely because lack of methods prevented demonstration of its existence generally in all deficiency diseases. More recently, the concept has taken on new meaning because tests have furnished evidence of its presence in several deficiency diseases.

In the laboratory, methods have been elaborated for detecting the latent state, as well as later stages, in the various specific deficiency diseases. In general, these tests fall into two groups: physiologic and biochemical. It is interesting that several of these physiologic tests have been in use for many years, long before deficiency diseases or vitamins were recognized, and consequently, long before the explanation of the test was known. For all deficiency diseases, both kinds of tests are theoretically possible; for some deficiency diseases, both tests are now available. But it should be explained that both types have not been developed for all deficiency diseases; nor where they are available, are they developed to the same degree. In some, the physiological test is at the moment superior; in others, the advantage rests with the chemical test.

This symposium will discuss, therefore, the latent state, its nature, significance, and implications for diagnosis; early manifest signs; and the physiologic and biochemical tests for certain deficiencies. My task is the least arduous, for I have only to ask questions, leaving the answers to my distinguished colleagues. Each of the guest artists is not only familiar with the field but has personally contributed to the advancement of some large portion of it.

Dr. Butler, what is the present status of the chemical estimation of vitamin A in the blood?

DR. A. M. BUTLER, BOSTON.—The chemical estimation of vitamin A in the blood is based upon determining the vitamin A concentration of plasma or serum. The blood cells contain very little carotenoids or vitamin A. The remarks that follow, therefore, refer to the analysis of plasma.

The lack of pure vitamin A has hampered the development of a completely satisfactory chemical method. Moreover, the reaction between vitamin A and the commonly used reagent for colorimetric analysis, namely, antimony trichloride, is

also inadequately understood. Furthermore, the reaction is not specific for vitamin A, and the color develops and fades so rapidly that the quantitative estimation of the reaction is difficult.

Despite these difficulties, however, the chemical estimation of vitamin A can be made with an accuracy that provides quantitative results of clinical significance. The color developed by the reaction of cod-liver oil preparations with antimony trichloride has been shown by Morgan and his associates to parallel the vitamin A potency although interfering substances are present. The pure vitamin A preparation of Holmes and his co-workers has a chromogenic property.

Without for the moment worrying about the correlation of colorimetric results with international units or blue units, Dr. May and Dr. Allen, in the Children's Hospital, have applied the methods of McCoord and Clausen for measuring $\beta$-carotene, xanthophyll, and total carotenoids plus vitamin A, to use with the photoelectric colorimeter. This photoelectric procedure provides several advantages. First, it permits accurate measurement of the maximum color developed in the course of this very quick reaction. Second, it permits the use of selective filters which increase the specificity of the reaction. Third, it permits the determination on 1 c.c. of serum of $\beta$-carotene, plus xanthophyll and total carotenoids plus vitamin A, and by difference, the apparent vitamin A.

Using pure $\beta$-carotene and pure xanthophyll, they have accurately calibrated the galvanometer readings in terms of these two substances for the yellow color of the carotenoid determination and for the antimony trichloride blue color. This permits correcting the galvanometer reading due to the total blue color to the reading due to the apparent vitamin A alone. To the galvanometer deflection reflecting this portion of the chromogenic substances, they have ascribed an arbitrary apparent vitamin A calibration.

With this method and arbitrary unit, May and Allen and May and McCreary have studied the apparent plasma vitamin A level in persons of different ages and patients with malnutrition, celiac disease, congenital obliteration of the bile duct, the lipemias of nephrosis, diabetes, and Von Gierke's and Pick-Neimann's diseases. They have studied the absorption of carotenoids and vitamin A and the conversion of the former into the latter and the effect of bile salts on absorption. Their results, which confirm and extend the observations of Clausen and associates, will be made available in a paper to be published in the near future.

I hope this brief outline answers the question in not too unsatisfactory a manner. Despite the limitations of the chemical analysis and of our inability to correlate the analytical results with units or milligrams of vitamin A, the method provides significant quantitative information concerning problems of clinical and physiologic interest.

CHAIRMAN KRUSE.—Dr. Jeans will discuss the technique of determining vitamin A deficiency by the detection of night blindness.

DR. P. C. JEANS, IOWA CITY.—Night blindness represents an inability to adapt vision to darkness. Functional night blindness depends on relative lack of vitamin A or its precursors in the retina. In the absence of demonstrable disease of the eye, poor dark adaptation is an acceptable criterion of vitamin A deficiency.

Various instruments are available for measuring ability to adapt to darkness. All are based on the same fundamental principles. The more common usage is to make measurements of adaptation to darkness after a period of controlled light adaptation. As soon as the bright light is extinguished, there is begun a series of measurements of the amount of light required to see a test object. With the passage of time in darkness, the amount of light required to see the test object rapidly decreases. A curve of these light values may be plotted and compared with curves obtained from examination of those persons known to be normal.

CHAIRMAN KRUSE.—Dr. Jeans, what tests have been found for the measurement of vitamin $B_1$, or thiamin chloride?

DR. JEANS.—Vitamin $B_1$, or thiamin, after ingestion becomes converted to thiamin pyrophosphate ester (co-carboxylase) and unites with a protein to form carboxylase, a catalyst or enzyme necessary for the oxidation of pyruvic acid, a normal and important intermediary in the breakdown of carbohydrates. When carboxylase, or its precursor thiamin, is deficient, metabolism of sugar is blocked at the pyruvic acid stage and pyruvic acid accumulates in the blood. While pyruvate appears to be harmless in itself, as in the case of acetone in moderate ketosis, its increase in the blood represents a metabolic dysfunction of cells which is ultimately reflected in the various clinical manifestations of vitamin $B_1$ deficiency.

One of the methods used for determining vitamin $B_1$ deficiency consists of estimation of the blood level of pyruvate and comparison of the values found with normal values. Conditions at the time of determination must be controlled carefully inasmuch as blood pyruvate is normally increased after brisk exercise. Increases as a result of exercise are moderate and temporary in normal persons, whereas in those with beriberi or vitamin $B_1$ deficiency the increases are greater and the return to normal is greatly delayed. Pyruvic acid may be determined specifically in small amounts of blood by colorimetric comparisons after the formation of a dinitro hydrazone.

Another method for determining vitamin $B_1$ deficiency consists of the comparison of the amount of thiamin excreted after a test dose with normal values previously established for the type of procedure employed. This method is comparable in principle with the similar method for determining the amount of vitamin C required for "saturation." In the use of this method it is customary to examine only the urine, although it is recognized that only a small proportion of ingested thiamin is excreted by way of the urine, some being destroyed in the body and some being excreted by bowel. Despite these various fates of ingested thiamin, urinary excretion seems to be quite sensitive to the amount ingested and changes in intake are promptly reflected in the excretion by this route.

A large amount of effort is being expended to devise simple accurate methods for determining thiamin in the urine and to establish suitable standards with which to compare the results. The multiplicity of the present methods speaks eloquently for the concept that no one of these has yet proved completely satisfactory. Present methods may be classified as of two main types, chemical and biologic.

The chemical methods consist of the production of changes of such a nature that a fluorometer or a colorimeter may be used in the determination. The most widely used chemical method is the extraction, adsorption, and elution of thiamin, with subsequent oxidation to thiochrome by ferricyanide, and the measurement of thiachrome by means of its blue fluorescence. Another chemical procedure consists of colorimetric determination after the formation of a diazo compound, first having converted phosphorylated thiamin (co-carboxylase) to thiamin by a phosphatase from yeast.

The biologic methods for determining thiamin are numerous. They include the use of some of the higher forms of animal life and of some of the lower forms of vegetable life. Some methods depend on either the prevention or the cure of polyneuritis. Thiamin may be determined by observing the rate of growth of yeasts, molds, or bacteria. This method is not wholly specific when urine supplies the test material because urine may contain growth-stimulating materials other than thiamin for lower forms of plant life; i.e., these organisms often have the capacity for synthesizing thiamin from simpler substances which may be contained in urine. When yeast is used, the test is made more specific by the addition

of nicotinic acid. For all of these organisms the test is made more reliable by determining the difference between activity before and after oxidation of thiamin with ferricyanide.

A test of greater qualitative than quantitative value consists of determination of the oxygen uptake in vitro of slices from the brain of a vitamin $B_1$ deficient pigeon in a pyruvate medium and in the presence of the test material.

In the literature are to be found data on the thiamin content of the urine in health and in vitamin $B_1$ deficiency. However, observers differ from each other in the amount of excreted thiamin reported as normal and abnormal. Probably not until methods for determining thiamin in the urine have been improved and different observers are able to obtain values of the same order of magnitude can the excretion of thiamin be used as a satisfactory guide to the vitamin $B_1$ status of the body.

The therapeutic test for vitamin $B_1$ deficiency has been tried repeatedly in clinical observations. In the case of obvious clinical manifestations recognized as being caused by vitamin $B_1$ deficiency, the therapeutic test produces striking curative results. For lesser degrees of deficiency and in instances in which perhaps little or no deficiency exists, therapeutic trial has given, and may be expected to give, results rather vague and difficult to interpret. For example, Poole, Hamil, Cooley, and Macy fed an evaporated milk formula to a control group of babies and the same diet plus an extract of rice polish to an experimental group. The control diet was of such a character that the vitamin $B_1$ content was presumably somewhat less than the theoretical requirement. The only observed difference between the two groups was that the babies receiving the vitamin B addition grew at a steadier, though not at a more rapid, rate. Other workers have reported for children a more rapid growth rate when the customary diet was supplemented with vitamin B complex.

The clinical studies of possible moderate deficiency leave much to be desired concerning evidence of specific deficiency of vitamin $B_1$. For the present it seems necessary to depend on the theoretical calculations of the human need for this vitamin and the supplying of foods containing amounts appropriate to meet this need.

DR. J. H. ROOT, WATERBURY, CONN.—Would you care to discuss the significance of the other eight components besides vitamin $B_1$?

DR. JEANS.—Riboflavin, nicotinic acid, and thiamin are the important ones.

CHAIRMAN KRUSE.—Dr. Butler, what methods have been developed for detecting the quantity of vitamin C in the blood, plasma, and urine? Are these methods satisfactory?

DR. BUTLER.—The answer to the last question is both yes and no. A general statement concerning methods will clarify the difficulty of giving a specific answer.

The commonly used chemical methods are based on the fact that in an acid solution, ascorbic acid alters the color of certain dyes by reducing them. The commonly used dyes are 2-6 dichlorophenolindophenol and methylene blue. Because the reduction of the latter is a more complicated reaction requiring exposure to strong light, the former dye is the indicator in common use in clinical laboratories. Unfortunately, substances other than ascorbic acid which may be present in blood, urine, and tissue reduce the indophenol dye. However, under the conditions of the analytical procedures, ascorbic acid reduces the dye more rapidly than these other substances. If the reduction is measured by titration, observation of this rate factor is not well controlled. For this reason, photoelectric colorimetry has been used instead of titration so that the rate of reduction could be observed. This method has been applied to serum or plasma analysis by Mindlin and myself, to urine analysis by Evelyn and co-workers, and to food analysis by Bessey.

It so happens that serum and plasma contain almost no interfering substances. They, therefore, can be analyzed in the absence of any hemolysis with sufficient

accuracy by the titrimetric procedure, if 2-c.c. samples are used. The macro-method of Farmer and Abt is satisfactory. Use of smaller samples, however, makes the titration unreliable. On the other hand, the photoelectric procedure gives satisfactory results with as little as a 0.1 c.c. sample.

In urine the concentration of interfering substances may be great enough to cause considerable error in the titrimetric procedure. Therefore, photoelectric colorimetry should be used.

The analysis of whole blood is rather difficult. Up to the present time most reported whole blood analyses must be looked on with skepticism. Probably skepticism should also be applied to many of the reported tissue analyses. Recently we have obtained two methods for the analysis of whole blood which seem satisfactory. However, they have been subjected to the acid criticism of others for only a short time.

Bessey, in one of the special articles in the *Journal of the American Medical Association* on vitamins, discusses the methods of assay of vitamin C at some length. Anyone interested in this aspect of the subject should refer to his paper for details and references.

CHAIRMAN KRUSE.—Dr. Butler, can deficiency or adequacy of vitamin C nutrition be estimated by analyses of blood or urine?

DR. BUTLER.—Before answering that question, it is best to discuss what is meant by a state of saturation and deficiency with respect to ascorbic acid. As first introduced and still commonly used, "saturation" is a state of supply of ascorbic acid such that, if the intake is increased, 60 to 80 per cent of the added ascorbic acid will be excreted in the urine within eight to twenty-four hours. Hence a person is unsaturated when but little increase in excretion follows an increase in the ascorbic acid intake. This does not mean that unsaturation is an abnormal state or that a supply inadequate to provide saturation indicates vitamin C deficiency. The majority of people, whom we today consider normal because they show no detectable signs of deficiency, are not saturated. Some day we may have evidence that this indicates a pathologic nutritional deficiency, but today the evidence is wanting. And now to answer the question by subdividing it. What can be learned from plasma analyses? We have already remarked that a single plasma determination is an unreliable index of saturation. However, if the dietary intake is known and if the patient has not just ingested ascorbic acid or been subjected to twelve hours of fasting, or less if an infant, then plasma levels of 0.8 mg. per cent or higher probably indicate satisfactory vitamin C nutrition. Fasting values above 1.2 mg. per cent probably indicate saturation. If, on the other hand, the plasma level is below 0.4 mg. per cent and no infection is present, the vitamin C nutrition may be, but not necessarily is, deficient. Ralli and co-workers put the optimal plasma level at from 1 to 1.2 mg. per cent. Certainly higher values seem unnecessary as they are not accompanied by increased retention, but merely increased excretion. Infection lowers the plasma level. Whether this lowering is associated with a threatened deficiency we do not know. Mindlin has shown that the plasma level of young infants falls very rapidly with a few hours of fasting. When one watches, as we have, an infant recover from acute scurvy, with the plasma level never rising above 0.2 mg. per cent, one wonders about the significance of plasma levels of 0.4 mg per cent. Finally, remembering that the limit of error of the method is 0.1 mg. per cent, plasma levels of 0.1 mg. per cent may be found in people who, as far as we can tell, have no evidence of deficiency or in people who have severe scurvy.

Tolerance tests which measure plasma values following the oral or intravenous administration of stated amounts of ascorbic acid have been described by Portnoy and Wilkinson, Wright and co-workers, Kjadi and others. They undoubtedly give information as to the vitamin C nutrition of the body.

What can be learned from urine analyses? The simplest test perhaps is the measurement of the daily urinary ascorbic acid excretion. Various workers have stated minimum normal values as being between 10 and 30 mg. per day. Not only does the amount vary with the method of analysis, but also with the protein content of the diet and the acid and base properties of the diet. However, it may be stated that excretions above 15 mg. per day suggest the absence of any deficiency. But a person excreting that amount may be almost saturated or very far from saturation. More accurate information may be obtained by measuring the urinary excretion during a saturation test. Undoubtedly, the amount of ascorbic acid required before saturation is reached, provided infection is absent, gives information concerning vitamin C nutrition. Time does not permit our going into details of these tests. But, if there were ample time, I could do no better than refer you to the excellent article by Sybil Smith on "Human Requirements of Vitamin C" in the *J. A. M. A.* special articles on vitamins already referred to (**111**: 1753, 1938). The description and appraisal of the methods, conclusions, and bibliography are excellent.

Third, what can be learned from whole blood analyses? We can start by repeating that most analyses probably have involved considerable error. It may be as much as 100 per cent. Because white blood cells may have from 20 to 100 mg. per cent apparent ascorbic acid, as shown by Stephens and Hawley, Kellie and Zilva, and Cushman and myself, a high whole blood level may reflect a leucocytosis which may or may not have some relation to C nutrition. On the other hand, there is much evidence supporting the contention of Van Eekelen, Emmerie, Heinemann, and others that whole blood levels are a better index of vitamin C nutrition than plasma levels. It was just this evidence that led us at the Children's Hospital in Boston to seek methods of analyzing whole blood, red cells, and white cells. Today we have the methods, but their application to estimating C nutrition is as yet too meager to warrant discussion.

CHAIRMAN KRUSE.—What are the daily ascorbic acid requirements of adequate nutrition?

DR. BUTLER.—Minimal and maximal requirements are available. From what has already been said, you can see that we have no real data concerning adequate requirements. Gothlin, using the capillary resistance test, and Widenbauer, using a urinary excretion test, estimated the requirements at the lower end of the scale as approximately 20 mg. per day for an adult weighing about 60 kg. Van Eekelen estimated the saturation requirements to be approximately 0.8 mg. per kilogram of body weight. The work of Everson and Daniels, however, suggests that the requirements parallel metabolic rate rather than weight. Available evidence seems to suggest that vitamin C should be added to the diets of artificially fed infants at birth, of mothers during pregnancy and lactation, and of children and adults not able to consume liberal amounts of fresh fruit. The daily requirement of from 5 to 15 mg. recommended by the Technical Committee on Nutrition of the Health Organizations of the League of Nations seems to be as much a thing of the past as the League itself.

Smith, after carefully appraising all the available information, concludes that barely adequate daily intakes are as follows: for infants, 20 mg.; children, 40 mg.; adults, 60 mg. Nursing mothers should be supplied with 100 mg. of vitamin C daily. The trend of evidence seems to indicate that our previous standards were too low.

CHAIRMAN KRUSE.—Dr. Butler will evaluate the capillary resistance test.

DR. BUTLER.—The capillary resistance test checks fairly well with the chemical tests; however, this is a physiologic test and many factors may make it less accurate than the chemical tests. Physiologic or capillary resistance tests were used many years before the discovery of vitamin C and chemical tests.

CHAIRMAN KRUSE.—I would like to ask Dr. Tisdall to tell this group about his experience with capillary resistance tests.

DR. F. F. TISDALL, TORONTO.—We have not found the capillary resistance tests satisfactory because so many other factors, especially ultraviolet light, have to be considered.

CHAIRMAN KRUSE.—Dr. Jeans will now discuss vitamin D deficiencies, with particular reference to calcium and phosphorus estimations.

DR. JEANS.—In a consideration of the clinical evidence of vitamin D deficiency, usually the first thought is of infantile rickets. The diagnosis of this disease would offer little difficulty were it not for certain reported observations in which rickets is said to exist in the presence of normal blood values for calcium and phosphorus, and in which roentgenograms are interpreted with a precision beyond the ability of the average pediatrist and with a leaning in the direction of the diagnosis of rickets unwarranted by concomitant findings. It is possible to interpret many of these observations in such a way as to eliminate some of the hypothetical difficulties in the diagnosis of rickets. In instances in which slight rickets has been diagnosed from x-rays by certain experts, there have been found not only normal blood values for calcium and phosphorus, but retention of these elements and rates of linear growth well above the average. It is believed that, with rapid rates of growth and high retention of calcium and phosphorus, the bone changes diagnosed by x-ray as representing slight rickets are not rachitic in character, but instead may perhaps represent normal changes incident to rapid growth.

In certain other instances in which rickets has existed in the presence of normal blood values for calcium and phosphorus, there seems always to have been associated antirachitic therapy; interpretation is complicated by consideration of the lapse of time from the beginning of therapy and the amount of vitamin D given. Blood values for calcium and phosphorus tend to become normal during the process of healing of rickets and before the healing is complete. In most cases of infantile rickets under treatment one can find a time when the x-rays still show evidence of rickets even though the blood values have become normal. This combination of findings should cause no confusion when it is known that therapy has been given and when it is realized that the blood values improve relatively early in the course of treatment.

When these various considerations are taken into account, our most reliable and clinically useful criteria for determining the presence or absence of rickets remain the roentgenograms of bones and the blood levels of calcium and phosphorus. In addition, phosphatase determinations are useful. The presence in the blood plasma of phosphatase above the normal levels and in association with characteristic changes in the roentgenogram and in the calcium and phosphorus levels of the blood would seem to establish the diagnosis beyond any reasonable doubt.

The mere prevention of clinically recognizable pathology is not to be accepted as a criterion of adequacy for any of the nutritional essentials. Rickets prevention alone, therefore, should not be considered as representing an appropriate and desirable intake of vitamin D. When three times the amount of vitamin D barely sufficient to prevent rickets is given, retentions of calcium and phosphorus and rates of linear growth are appreciably increased. The detection of vitamin D deficiency under circumstances in which infantile rickets has been prevented is an expensive, laborious, and time-consuming undertaking, one which can be carried out for the purpose of studying general trends with only a limited number of babies. Nevertheless, it is to be emphasized that moderate vitamin D deficiency may exist in a baby who has no evidence of rickets.

Because the absence of rickets has been rather generally accepted as an indication of the nonexistence of vitamin D deficiency and because the child beyond

infancy does not have rickets under usual circumstances, there is noted a tendency to a belief that the child does not need vitamin D from special sources and that no deficiency ordinarily exists. Several types of observations attest to the fact that vitamin D deficiency is relatively frequent in childhood. Seasonal variation in growth is dependent in a large measure on the variation in the amount of vitamin D available. When vitamin D is supplied throughout the year, seasonal variations in growth tend to disappear. Dental caries is widely prevalent, and observations repeatedly have shown that vitamin D is one of the important factors in its prevention. Balance experiments have shown that for many children vitamin D is necessary for the retention of the amount of calcium and phosphorus required to maintain the theoretically normal mineralization of the skeleton.

Although we know that vitamin D is needed by most children throughout the period of growth, we have no easy way of determining vitamin D deficiency in the child. The methods available are too laborious for general application. Estimation of vitamin D deficiency in childhood remains in the province of the research worker. In clinical practice this deficiency is something rather vague and nebulous. However, the facts established by research should be applied in clinical practice. It is known that some children are quite efficient in the utilization of ingested calcium and phosphorus and do not need vitamin D from special sources; for many children, vitamin D is essential for the maintenance of normal mineral metabolism. Because it is not possible to determine readily to which of these two classes a child belongs, it is preferable that all children receive an amount of vitamin D adequate for those less efficient in calcium utilization.

DR. J. E. DYSON, DES MOINES.—Is there an optimum vitamin D dosage? Is there a danger of overdosage?

DR. JEANS.—It is our opinion that from 300 to 600 units daily are adequate. Doses larger than 1,800 units daily may produce an adverse effect on the appetite and growth rate. The minimum standard U. S. P. oil has about 300 units to the teaspoonful. Most of the commercial oils have from 400 to 900 per teaspoonful. It is customary to prescribe 2 or 3 teaspoonfuls, but such doses are unnecessary.

DR. W. W. NICHOLSON, LOUISVILLE.—Does it take massive doses of cod-liver oil to promote healing in some cases?

DR. JEANS.—There are some cases refractory to cod-liver oil, but these are not usually true cases of infant rickets. In such cases the preventive dose is also the therapeutic dose.

DR. BUTLER.—The exceptional cases may heal with very large doses of cod-liver oil; however, there is a narrow margin between the maximum therapeutic dose and the overdose. These overdoses may produce the excessive elimination of calcium through the kidneys and may, therefore, be potentially dangerous. We watch the urine by simple test reported by Albright and Culkovich. In this test a simple reagent is used to test for calcium precipitated in the urine. We have encountered two patients from one family who required large doses of vitamin D. The bones showed rickets in the x-rays during childhood, but after many years the picture of hyperparathyroidism appeared.

QUESTION.—An occasional baby who has had a sufficient amount of cod-liver oil since 4 to 5 weeks of age, sometimes develops clinical symptoms of rickets at a later age. Do these babies absorb their cod-liver oil properly, or are these true cases of rickets?

DR. JEANS.—This depends on the clinical and x-ray diagnosis of rickets. We cannot rely on the clinical diagnosis of rickets. Repeatedly, babies with clinical

rickets are found to have no rickets if calcium and x-ray studies are made. It is not safe to make diagnosis on the clinical picture alone.

DR. SIEMSEN, CHICAGO.—Is the single therapeutic dose in the treatment of rickets effective?

DR. JEANS.—Foreign reports indicate that the single dose may be effective, but it is not justified unless you do not expect to see your patient again.

DR. H. F. HELMHOLZ, ROCHESTER, MINN.—Does fortification of milk satisfy the requirements for the period beyond infancy?

DR. JEANS.—There are two unitages in fortified milk, 135 and 400. The 135 unit milk, although it prevents rickets, is not wholly adequate during the growth period. Assuming an intake of 1½ to 2 pints a day, 400 unit milk is adequate.

DR. B. S. VEEDER, ST. LOUIS.—I have trouble getting adolescent girls to drink milk. Are calcium tablets fortified with vitamin D satisfactory in those cases?

DR. JEANS.—It is practical to substitute one calcium carrier for another. However, we must not forget there are other valuable constituents in milk.

CHAIRMAN KRUSE.—I would like Dr. Jeans to tell us something about calcium requirements and methods of determining calcium deficiencies.

DR. JEANS.—The calcium requirement increases gradually during infancy until, at 1 year of age, it is approximately 1 Gm. daily. It remains at this level for the next two years. From 3 to 5 years of age the requirement is from 0.6 to 0.7 Gm. daily, and after 5 or 6 years the requirement is at least 1 Gm. daily. These requirements are amply satisfied in infancy when milk is fed in customary quantities. From 1 to 3 years of age the requirement is satisfied by inclusion in the diet of at least 1½ pints of milk; from 3 to 6 years, by inclusion of 1 pint of milk; and over 6 years, by the inclusion of 1½ pints of milk, with preference of the inclusion of 1 quart.

The quantities of milk mentioned have been established as desirable by means of balance experiments in which has been determined the amount of calcium retained by the body at different age periods when various amounts of milk have been included in the diet and when the amounts retained have been compared with theoretically normal retentions. It is to be understood that, in order to attain the desired retentions with the stated intakes, vitamin D must also be included in the diet. Considerable variation exists in the efficiency of different children in the utilization of ingested calcium, so that the amounts of calcium stated as desirable are those required by children less efficient. While 1 pint of milk is insufficient for most children over 6 years of age, some children are found for whom this quantity is adequate when vitamin D is supplied as well.

The results of calcium deficiency are not easily apparent by clinical examination. Perhaps it is for this reason that calcium deficiency is not often given the consideration by the clinician that it deserves. The evidences of calcium deficiency are either vague or difficult to correlate definitely with the cause. Perhaps the most outstanding effect is the production of tooth decay. Tooth decay is rather definitely related to the amount of calcium retained. Retention is dependent on the intake of both calcium and vitamin D. In controlled studies of dental caries among institutional children, improvement in the condition of teeth is found when either vitamin D or milk is added to the institutional diet, and the best results are obtained when both additions are made. Emphasis is to be placed here on the fact that improvement occurs when milk alone is added to the diet.

A relationship between calcium retention and the rate of linear growth has been shown definitely for the infant and is indicated very strongly, if not proved, for

the child. Despite retentions of calcium moderately below those postulated as normal, linear growth may proceed at the average rate, but with mineralization of bone decreased below that of better-fed children. Ultimately, when growth is attained and the calcium requirement should be only that of maintenance, the bones gradually acquire their normal proportion of mineral, even with continuance of a relatively low intake. During the period of adolescence, however, actual osteoporosis may be observed with some frequency if roentgenograms are made routinely.

In considering these various manifestations of calcium deficiency, it is obvious that the deficiency is not to be detected by any clinical means commonly or easily employed. It is possible to determine extreme degrees of deficiency by obtaining knowledge of long-continued deprivation or by discovering definite osteoporosis. The only exact and satisfactory method is observation of the calcium metablism over a protracted period of time. It is well known that the blood level of calcium ordinarily gives no clue to the calcium status of the body, since the body is able to maintain a relatively normal blood level even with a negative calcium balance.

Lacking a clinically applicable method for detecting calcium deficiency and recognizing the importance of adequacy of calcium for bone and tooth growth and normality, the best procedure is to make certain that an ample amount of calcium is being ingested at all times. It is to be emphasized that vitamin D, although helpful in calcium utilization, cannot compensate for an inadequate intake of calcium. No amount of vitamin D can produce an adequate retention of calcium from an inadequate intake. Apparently, vitamin D has no effect on calcium retention when the calcium intake is less than approximately one-half the requirement. The idea that vitamin D improves a diet low in calcium is both prevalent and fallacious.

DR. TISDALL.—In regard to calcium, we know fairly well the amounts necessary for optimal levels. What does Dr. Jeans feel about the levels in older children? What about the period of rapid growth?

DR. JEANS.—The field of calcium metabolism in adolescents is practically untouched. From one report there is shown the need of calcium and vitamin D. The needs are fully as great, if not greater, in adolescents. There is a great need for research here.

DR. E. T. McENERY, CHICAGO.—What type of calcium is most easily assimilated in children?

DR. JEANS.—Any type of calcium may be utilized in the body, but it is necessary for phosphorus to be taken along with it. Fortunately, phosphorus is usually present in adequate amounts in the average diet. Dicalcium phosphate and other calcium compounds are as well assimilated as milk.

CHAIRMAN KRUSE.—We shall now discuss our last nutritional essential, iron. I would like to ask Dr. Guest what he considers adequate levels of hemoglobin and red blood cell counts in the blood of infants and children.

DR. GEORGE M. GUEST, CINCINNATI.—It is important to express hemoglobin values in terms of grams of hemoglobin per 100 c.c., instead of in terms of percentage as is commonly done. It is noted that values in optimum and average groups had almost identical findings up to the age of 10 months, but in the more favored economic groups the values tended to be higher. In the first 6 to 10 months of life, the appearance of microcytosis gives a clue to the later appearance of a nutritional anemia.

In answer to the question, "What is the optimum hemoglobin value in childhood—11 or 13 Gm.?" I am not prepared to give an arbitrary standard.

Our chairman has asked for a discussion of certain hematologic methods that may be used in the diagnosis of nutritional anemia. Some of the more funda-

mental aspects of the subject of iron deficiency in relation to this type of anemia are to be dealt with in other round table discussions scheduled for these meetings.

Accurate methods for the determination of the number of red blood cells and the amount of hemoglobin in blood have been available for a long time. Nevertheless, even after the most careful application of these methods in hematologic studies of infants and children, it is difficult to decide what levels of hemoglobin and red cell count can be considered optimal, suboptimal, average, or merely slightly low. Extremely low values found in infants with severe anemia are, of course, easily recognized. It is the borderline between the high and low "normal" values that needs most attention at the present time. In addition to the red cell count and hemoglobin levels in whole blood, data on the mean size and hemoglobin content of the erythrocytes are being recognized as increasingly important and sensitive criteria of the development or existence of nutritional anemia.

Wide variability in these characteristics of the red blood cells may be found among seemingly normal infants at different ages. The establishment of hematologic standards necessitates the evaluation of this variability among both anemic and nonanemic infants, and of various factors which may influence the number and the character of the erythrocytes in the blood.

As examples of observations already made in studies of this problem, I shall present some charts* showing hematologic data on 1,070 samples of blood drawn from approximately 600 infants and children ranging in age from birth to 5 years. These data represent, we believe, a fair cross section of the child population of Cincinnati, including all economic levels and infants and children in different states of health—sick and well, anemic and nonanemic, institutional and family groups, etc., excepting, however, prematurely born infants and those with primary blood dyscrasias. None of the infants had received iron other than that in their diets prior to the taking of the blood samples. These scatter charts show graphically the age periods in which were found notable changes in red cell count and hemoglobin in whole blood, the mean size and hemoglobin content of the red blood cells at different ages, and the directional trends of the changes in those values which were found commonly occurring at different ages. The methods used in these studies, and the terminology, are fully described elsewhere.†

*Red Blood Cell Count.*—At birth, the cell counts ranged between 4 and 6.5 millions per cubic millimeter, with a mean of 4.8 millions. After the first ten days or so, the average cell count decreased rapidly for from two to three months. At three months, counts of 3.5 to 4 millions were seen frequently. After this age, the cell count tended to increase and attained an average of 4.8 millions toward the end of the first year. The greatest variability was seen at ages from 6 to 18 months, with counts ranging from 3 to 6 millions.

*Hemoglobin in Whole Blood.*—As is well known, the hemoglobin in blood is high at birth. In our observations, the mean of values determined in eighty-nine samples from infants aged 1 to 10 days was 19 Gm. per 100 c.c. During the first two to three months these values fell rapidly, corresponding to the decrease in cell count, to reach below 10 Gm. in many instances. In most infants a sharp rise in the hemoglobin content of the whole blood was noted between the second and fourth months, followed by a secondary fall in those infants who went on to develop varying degrees of anemia. The highest incidence of low values, found in infants with most marked anemia, was found at ages between 8 months and 2½ years. The average value for the entire group at 1 year of age was 11.0 Gm. per 100 c.c., while in an "optimum" group (from families of higher economic levels), the average was 12.5 Gm. per 100 c.c.

*Charts 1, 3, 5, 7, 9, and 13. Guest, G. M.; Brown, E. W.; and Wing, M.: Am. J. Dis. Child. 56: 529, 1938.

†See Guest, Wing, and Brown, loc. cit.

*Red Blood Cell Size.*—The mean volume of the red blood cells at birth was around 115 cubic micra, with values ranging between 90 and 120 cubic micra. After the first few days, the cells decreased rapidly in size, until at about 6 months the average was around 75 cubic micra. Marked microcytosis, indicated by values of 60 cubic micra or less, was seen most frequently at ages between 8 and 27 months. The infants with these values often enough had clinically recognizable anemia, but it is important to note that anemia had not been suspected in many of the infants whose red blood cells showed this degree of microcytosis. In 173 samples of blood from infants around 3 years of age, the mean size of the red cells was 78 cubic micra.

*Hemoglobin Concentration in the Cells.*—The concentration of hemoglobin, expressed in grams per 100 c.c. of packed cells, is the true index of coloration or "-chromia." In children over 3 years of age, this value averages around 34 Gm. per 100 c.c. Marked variability in this characteristic of the cells was seen at birth, moderate hypochromia being seen not infrequently. This variability among different samples tended to diminish during the first 2 or 3 months, with actual increases in the average concentration during this period when the cells were diminishing in size. After 3 months, however, the average values tended to decrease. Lowest values were found in the second year. Values below 28 Gm. per 100 c.c., found in infants with severe anemia, were practically limited to the age period between 8 months and 2½ years.

*Mean Hemoglobin Content per Cell.*—The mean hemoglobin content of the red cells at birth is around 37 micromicrograms. In the cells of older children and adults, this value is around 29 or 30 micromicrograms. As an indication of microcytosis and/or hypochromia, this figure is the most easily obtained and the most practical for routine clinical work. During the first 6 months, the mean size of the cells diminishes, without much change in the hemoglobin concentration of the cells. After 6 months, the increasing tendency to development of microcytosis and hypochromia leads to an increasingly frequent occurrence of low values for the mean hemoglobin content per cell, this becoming most pronounced in the middle of the second year. Values below 20 micromicrograms, indicating more severe degrees of anemia, were found most frequently at ages between 8 months and 2½ years.

*Nutritional Anemia.*—In the so-called nutritional anemia, of the iron-deficiency type, the red cell count may be normal, high, or low. With a high cell count (possibly due to a physiologic effort to compensate for the deficiency), the hemoglobin content of the whole blood may not be much, if any, below what may be considered normal. However, the size and hemoglobin content of the cells, and hemoglobin concentration of the cells, are always low. Microcytosis and hypochromia of the cells are the most sensitive indicators of the development of this type of anemia, and of these, the microcytosis is the earlier to develop. When iron is administered in adequate doses, all values improve, approaching normal levels rapidly. The pattern of the changes, increasing size and hemoglobin content of the cells, and increasing concentration of hemoglobin in the whole blood, is the same at whatever age iron therapy is started.

Such observations as these which have been presented here emphasize the fact that we must divorce ourselves from the term "average" to define "normal" values for physical and chemical measurements, and think in terms of zones of values found in persons observed in apparently normal or optimal conditions. It is still difficult to say what is the optimal level of hemoglobin in the blood—whether, for example, 13 Gm. is better than 11 Gm., at the age of 2 years. The fact that the administration of iron may push these values to the upper limit is not necessarily proof that the additional iron is needed by the infant. This question must be left open for future investigation.

In answer to a question concerning the necessity for routine administration of iron to infants: Factors which may influence the development of nutritional anemia

may be listed briefly. A too long continued exclusive milk diet is a frequent cause, but the anemia often develops in infants offered a well-balanced diet in which iron-containing foods are introduced early. Maternal factors are being increasingly recognized as important. The relationship of maternal health, generally, and of the anemias of pregnancy, in particular, to the development of anemia in these infants is a most important part of this problem and one that deserves much more attention from both obstetricians and pediatricians than has been given to it in the past. Whenever the diagnosis of anemia is made in one child, inquiry should be made about the siblings, and iron should be given routinely to the succeeding siblings as prophylaxis against anemia in those infants. The mother of the anemic infant should be warned that her next infant will probably develop the same sort of anemia, and to prevent this, the administration of iron should be started early. In a succeeding pregnancy, it is wise to give such a mother iron during her pregnancy, even though the hemoglobin content of her blood is not thought to be unusually low.

DR. MENDEL ZELIGS, CINCINNATI.—Is it necessary to supply iron to all babies from the age of 6 months to 1 year? What type of iron? Is there sufficient iron in such cereals as pablum?

DR. GUEST.—There is no evidence that a moderate excess of iron does any harm. I might refer you to three papers by Josephs of Johns Hopkins in the January, February, and April issues of the *American Journal of Diseases of Children*. We should warn mothers with one anemic infant to give iron to succeeding infants. The type of iron is not important so long as enough is given. Iron ammonium citrate and ferrous sulfate are most used. We give 2 mg. per kilogram as the lower limit and 10 mg. as the upper.

DR. DYSON.—In the prevention of nutritional anemias, is it necessary to give iron, or are egg yolk and other foods satisfactory?

DR. GUEST.—It is necessary to give iron. We have seen nutritional anemia develop in infants given foods containing plenty of iron. Several children with a tendency to microcytosis anemia were followed over a period of time and all of these required iron.

DR. W. W. WESTON, COLUMBIA, S. C.—What is your choice of iron therapy?

DR. GUEST.—This is a difficult question to answer. We have used chiefly iron and ammonium chloride and also ferrous sulfate. The amount of iron is the most important factor, and also whether it is tolerated by the stomach.

# News and Notes

The 1941 meeting of the **Academy** will be held at the Statler Hotel, Boston, October 9, 10, and 11.

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At the annual meeting of the **American Board of Pediatrics** held in Memphis on Nov. 16 and 17, 1940, the following action was taken in regard to military service in the army or navy:

> Candidates for examination by this Board may substitute one (1) year of military service for one of the required two years of pediatric practice and/or continued study. Military service *cannot* be substituted for any of the required preliminary hospital training, but this preliminary training may be completed after return from military service.

Dr. C. Anderson Aldrich, secretary, 707 Fullerton Ave., Chicago, Ill., will be glad to answer any specific questions in regard to this ruling.

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The eighteenth annual meeting of the **American Orthopsychiatric Association,** an organization for the study and treatment of behavior and its disorders, will be held at the Hotel Pennsylvania, New York, N. Y., on Feb. 20-22, 1941. A registration fee will be charged for nonmembers. The preliminary program will be sent on request.

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The **American Board of Pediatrics** will hold an examination at Boston on Oct. 12, 1941, immediately following the national meeting of the American Academy of Pediatrics. No further applicants can be accepted for the examination at New York in March, 1941, because the list is now closed.

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## Calendar of Pediatric Meetings, 1941

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| March | 27-29 | Thu.-Sat. | **Meeting, Region I, A.A.P.**<br>(Dr. Oliver L. Stringfield, 1416 Bedford St., Stamford, Conn.) | **New Haven**<br>(Hotel Taft) |
| | 29-30 | Sat.-Sun. | **Examination, American Board of Pediatrics**<br>(Dr. C. A. Aldrich, 707 Fullerton Ave., Chicago, Ill.) | **New York** |
| April | 24-25 | Thu.-Fri. | **Meeting, Region II, A.A.P.**<br>(Dr. J. B. Stone, 2042 Park Ave., Richmond, Va.) | **Richmond, Va.**<br>(Hotel John Marshall) |
| May | 1-3 | Thu.-Sat. | **Meeting, Region IV, A.A.P.**<br>(Dr. Crawford Bost, 490 Post St., San Francisco) | **San Francisco**<br>(Fairmount Hotel) |
| | 15-17 | Thu.-Sat. | **Meeting, Region III, A.A.P.**<br>(Dr. Edward A. Wishropp, 10 Peterboro Ave., Detroit, Mich.) | **Chicago**<br>(Palmer House) |
| | 18 | Sun. | **Examination, American Board of Pediatrics** | **Chicago** |
| | 22-24 | Thu.-Sat. | **American Pediatric Society**<br>(Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis, Mo.) | **Hot Springs, Va.**<br>(The Homestead) |
| June | 4-6 | Wed.-Fri. | **Section on Pediatrics, A.M.A.**<br>(Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.) | **Cleveland** |
| Oct. | 9-11 | Thu.-Sat. | **Meeting, American Academy of Pediatrics**<br>(Dr. Clifford Grulee, 636 Church St., Evanston, Ill.) | **Boston**<br>(Statler Hotel) |
| | 12 | Sun. | **Examination, American Board of Pediatrics** | **Boston** |

The name under each meeting is that of the person in charge of the program and arrangements. Communications regarding hotel reservations should be sent directly to the respective hotels.

# Comments

The Tenth Annual Meeting of the Academy at Memphis in November was probably the largest group of pediatricians ever assembled in the United States.

The first E. Mead Johnson Award was made to Dr. Robert E. Gross of Boston for his work on patent ductus arteriosus, and the second to Dr. Lee E. Farr of Wilmington, Del., for his work on protein metabolism in nephrosis. The program one morning was largely given over to a symposium on virus diseases, with papers by Dr. Stimpert of Detroit, Dr. Goodpasture of Nashville, and Dr. Stokes of Philadelphia.

The regional and committee reports which were published in the JOURNAL last month show the multitude of activities in which the Academy is engaged. We particularly call attention to the report of Dr. Bevan of Rochester on the Academy activities in Northern New York. The Committee on Central and South American Scholarships appointed last year reported that six scholarships have been obtained for Argentina, Brazil, Chile, Cuba, Mexico, and Uruguay. The awards will be made through the national pediatric societies in those countries. The report of the Committee on Immunization Procedures has already been printed in pamphlet form and distributed. The Committee on Vitamins has prepared a pamphlet on what is known of the vitamins of clinical interest to the pediatrician, which will be published and distributed. A radical revision of the organization of the Council for Pediatric Research was announced, but a complete report is not available.

Dr. Richard M. Smith of Boston entered on his term of office as president, and Dr. Edward A. Mitchell of Memphis, Chairman of Region II for the past eight years, was made vice-president. A new office, Historian, was approved, to which Dr. Ernest Caulfield of Hartford, Conn., was elected. Boston was selected as the meeting place for 1941.

Particular credit for the success of the meeting is due to Dr. Grulee and Dr. Martmer for the splendid way in which it was organized and handled, and to the Memphis hosts for their far-famed "southern hospitality" which helped make the meeting one that will long be remembered.